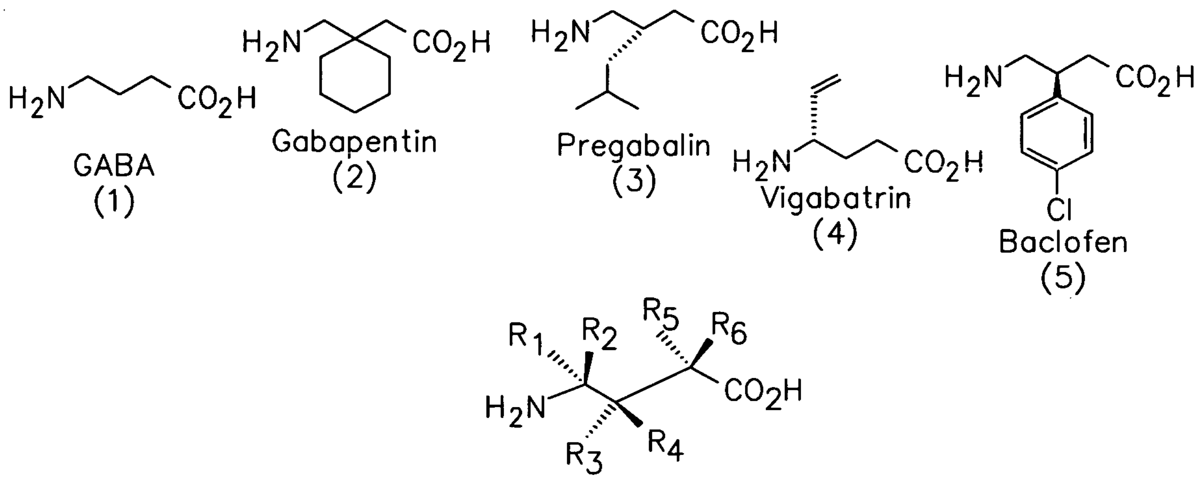
#3

FIG. 1



GABA (1)

Gabapentin (2)

Pregabalin (3)

Vigabatrin (4)

Baclofen (5)

Generalized GABA Analog (IV)

FIG. 2

The Enterohepatic Circulation with Key Transporter Proteins Mediating Bile Acid Circulation

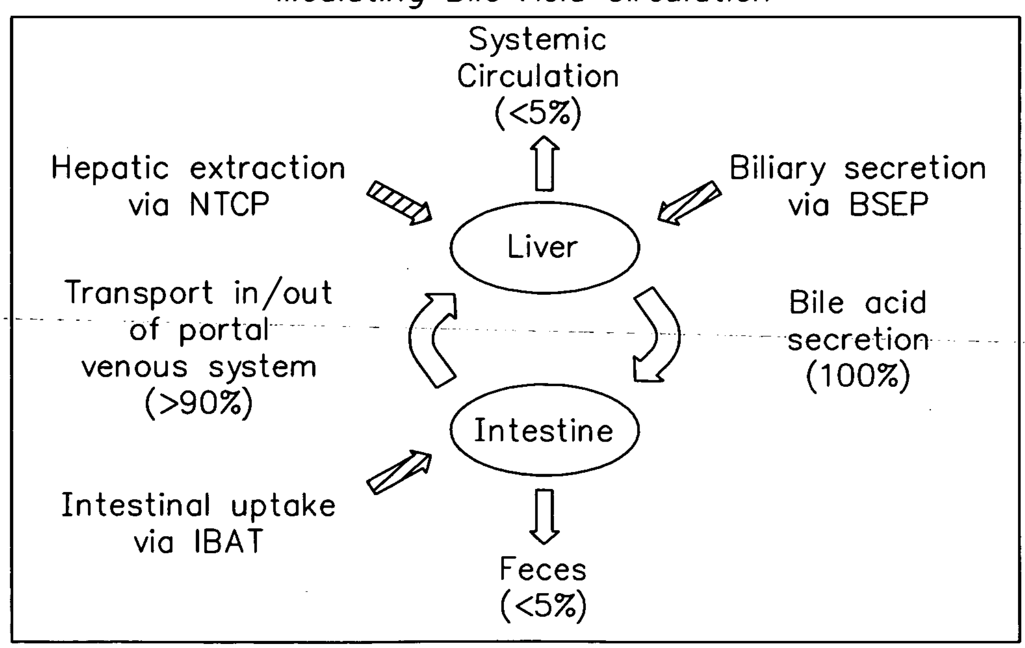
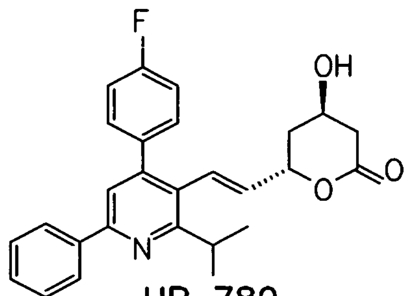
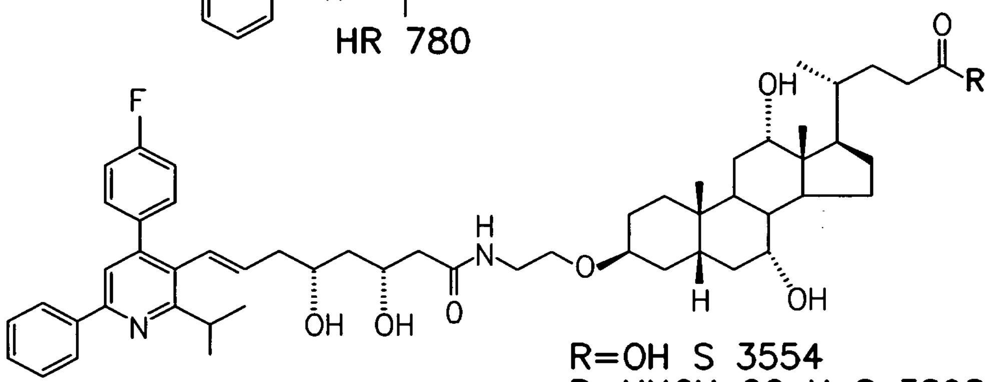


FIG. 3

Bile Acid Conjugates of HMG–CoA Reductase Inhibitor

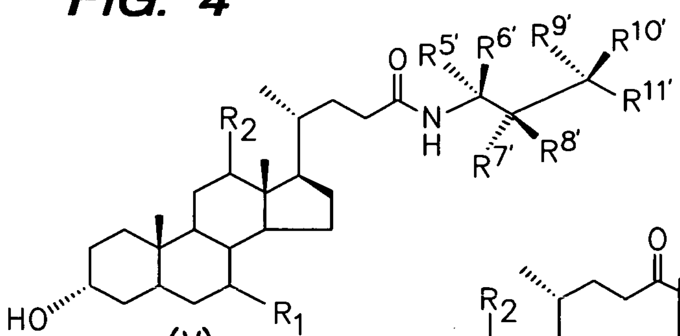


HR 780

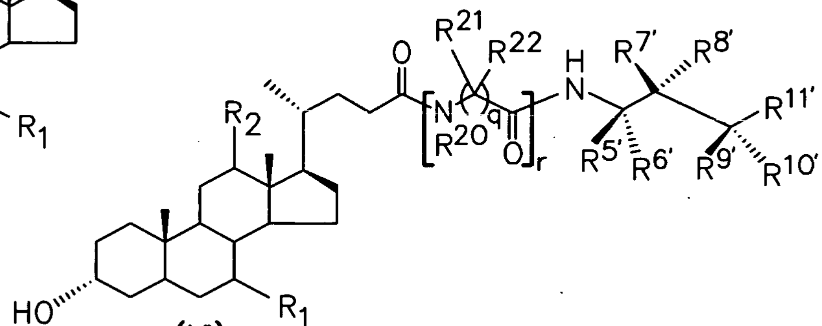


R=OH S 3554
R=NHCH$_2$CO$_2$H S 3898
R=NHCH$_2$CH$_2$SO$_3$H S 4193

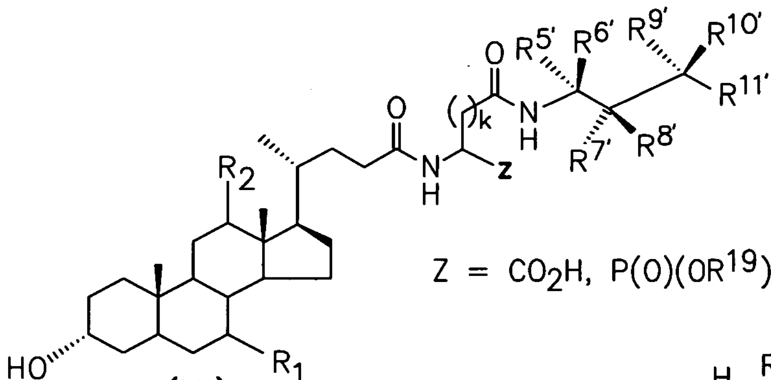
FIG. 4



(V)

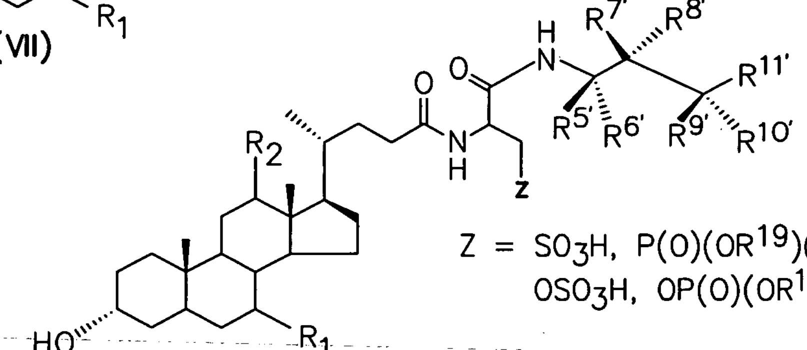


(VI)



Z = CO_2H, $P(O)(OR^{19})(OH)$

(VII)

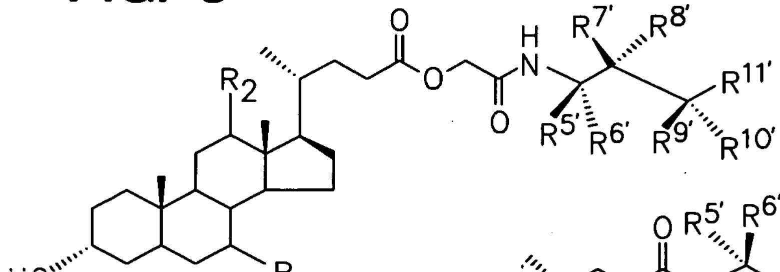


Z = SO_3H, $P(O)(OR^{19})(OH)$, OSO_3H, $OP(O)(OR^{19})(OH)$

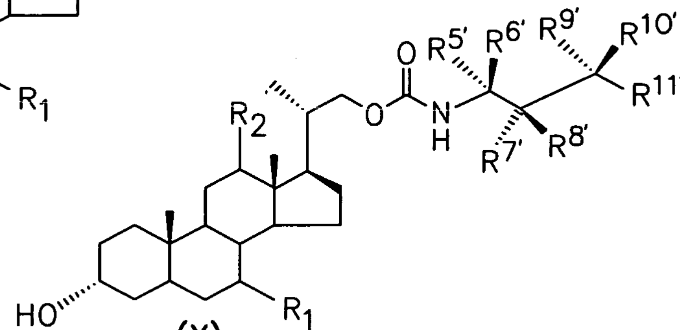
(VIII)

R1 = α-OH; R2 = α-OH (Cholate)
R1 = β-OH; R2 = H (Ursodeoxycholate)
R1 = α-OH; R2 = H (Chenodeoxycholate)
R1 = H; R2 = α-OH (Deoxycholate)
R1 = β-OH; R2 = α-OH (Ursocholate)
R1 = H; R2 = H (Lithocholate)

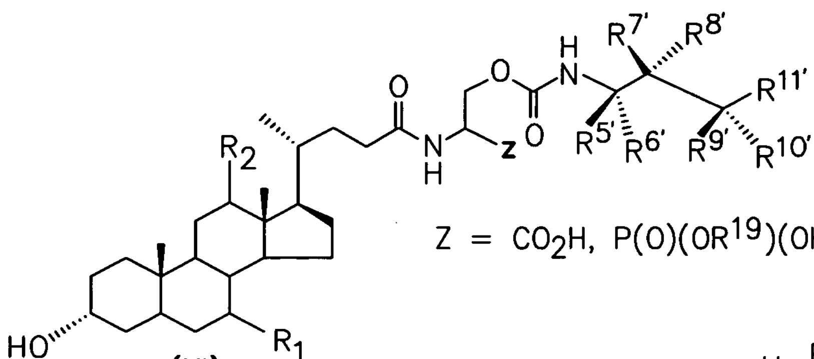
FIG. 5



(IX)

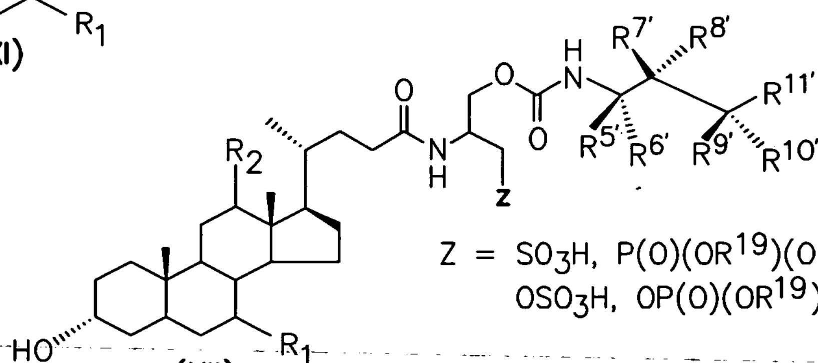


(X)



$Z = CO_2H,\ P(O)(OR^{19})(OH)$

(XI)

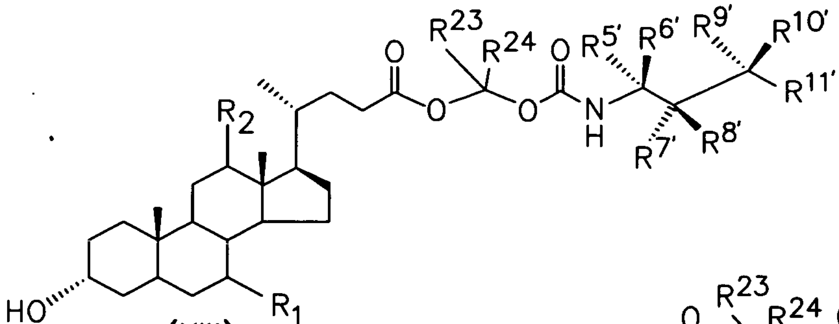


$Z = SO_3H,\ P(O)(OR^{19})(OH),\ OSO_3H,\ OP(O)(OR^{19})(OH)$

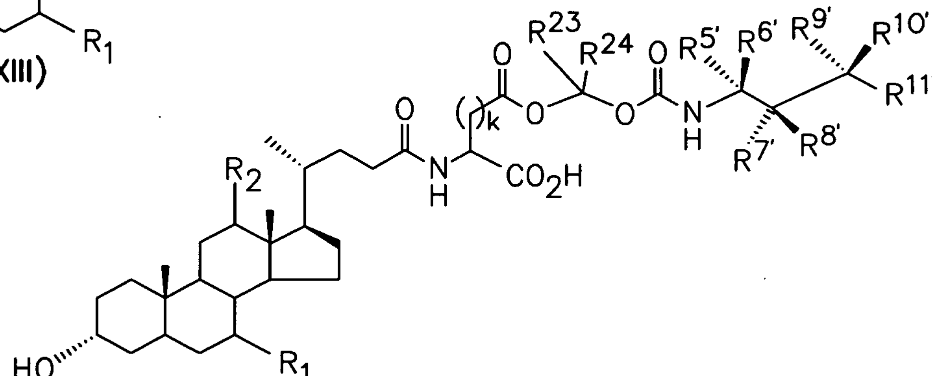
(XII)

R1 = α−OH; R2 = α−OH (Cholate)
R1 = β−OH; R2 = H (Ursodeoxycholate)
R1 = α−OH; R2 = H (Chenodeoxycholate)
R1 = H; R2 = α−OH (Deoxycholate)
R1 = β−OH; R2 = α−OH (Ursocholate)
R1 = H; R2 = H (Lithocholate)

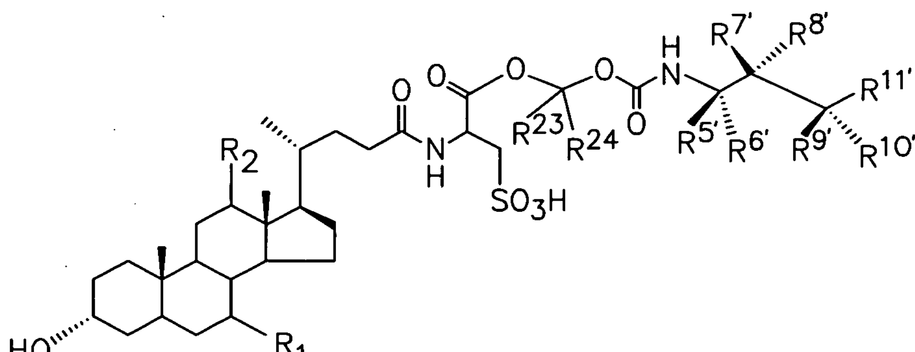
FIG. 6



(XIII)



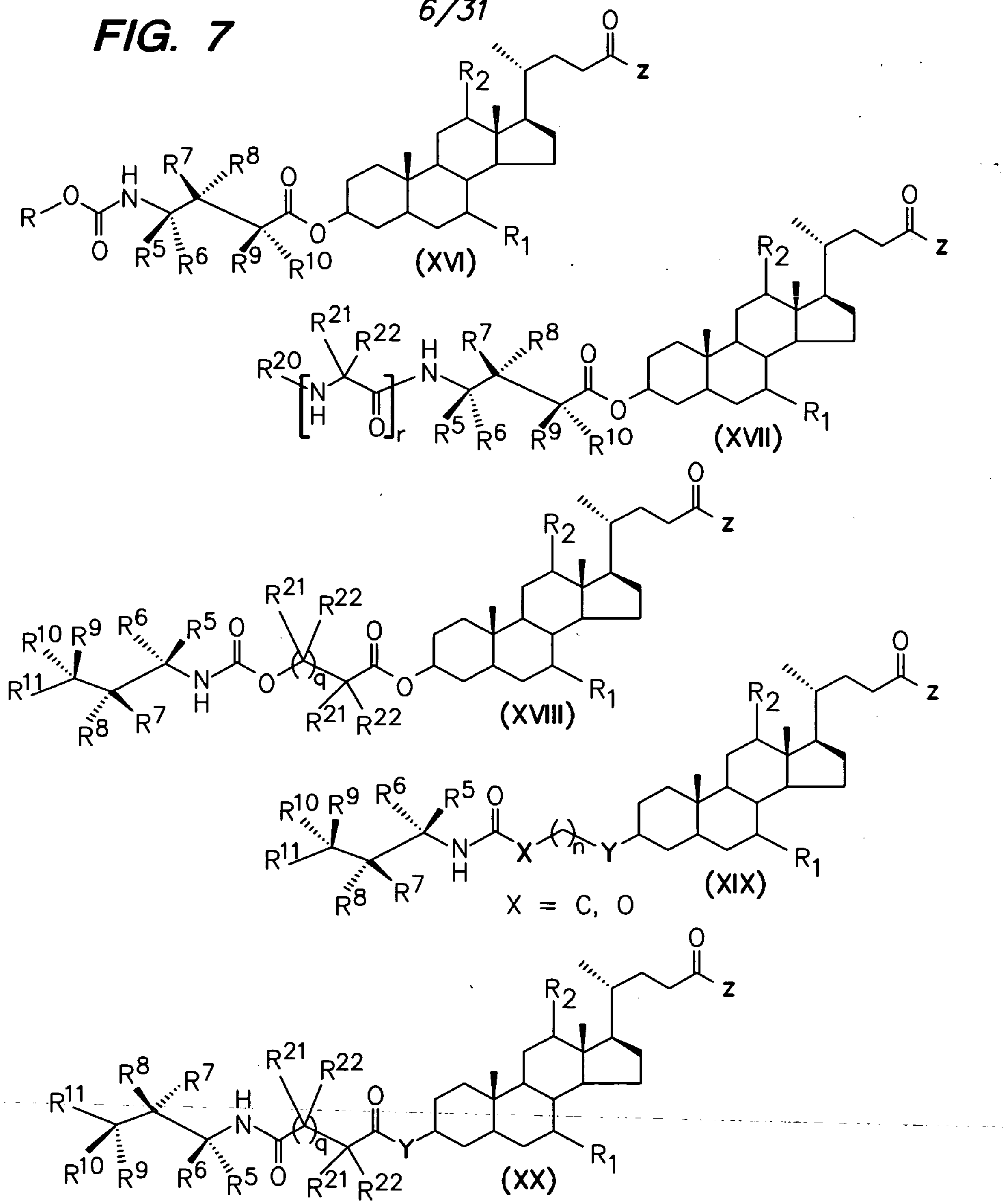
(XIV)



(XV)

R1 = α−OH; R2 = α−OH (Cholate)
R1 = β−OH; R2 = H (Ursodeoxycholate)
R1 = α−OH; R2 = H (Chenodeoxycholate)
R1 = H; R2 = α−OH (Deoxycholate)
R1 = β−OH; R2 = α−OH (Ursocholate)
R1 = H; R2 = H (Lithocholate)

FIG. 7



R1 = α–OH; R2 = α–OH (Cholate)
R1 = β–OH; R2 = H (Ursodeoxycholate)
R1 = α–OH; R2 = H (Chenodeoxycholate)
R1 = H; R2 = α–OH (Deoxycholate)
R1 = β–OH; R2 = α–OH (Ursocholate)
R1 = H; R2 = H (Lithocholate)

Y = α–O
Y = β–O
Y = α–NH
Y = β–NH

Z = OH

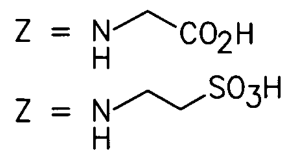
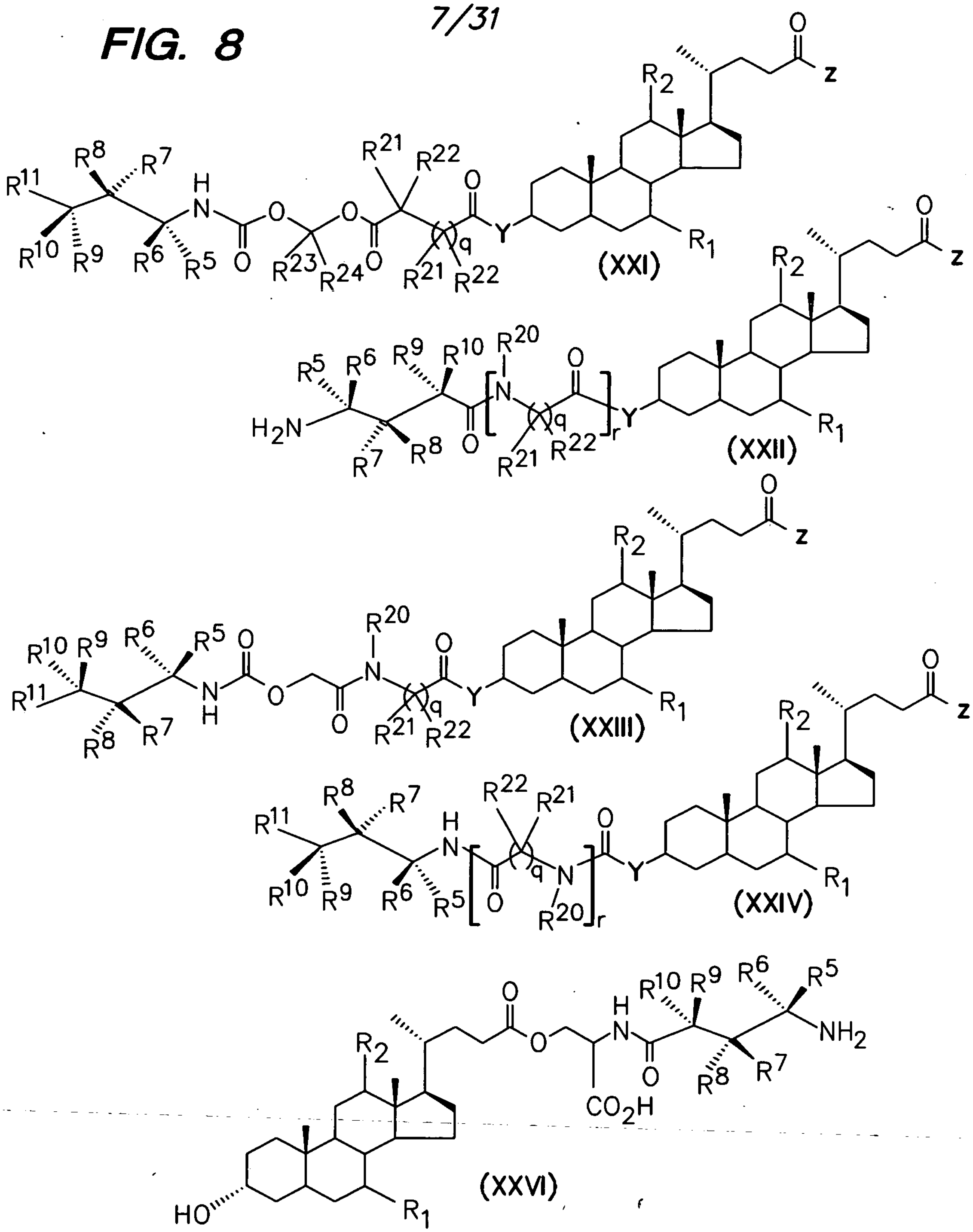


FIG. 8



R1 = α–OH; R2 = α–OH (Cholate)	Y = α–O	Z = OH
R1 = β–OH; R2 = H (Ursodeoxycholate)	Y = β–O	Z = NH–CH₂–CO_2H
R1 = α–OH; R2 = H (Chenodeoxycholate)	Y = α–NH	Z = NH–CH₂CH₂–SO_3H
R1 = H; R2 = α–OH (Deoxycholate)	Y = β–NH	
R1 = β–OH; R2 = α–OH (Ursocholate)		
R1 = H; R2 = H (Lithocholate)		

FIG. 9 Uptake of (8) (XP10569) or Glycochocholate by IBAT-Transfected CHO Cells

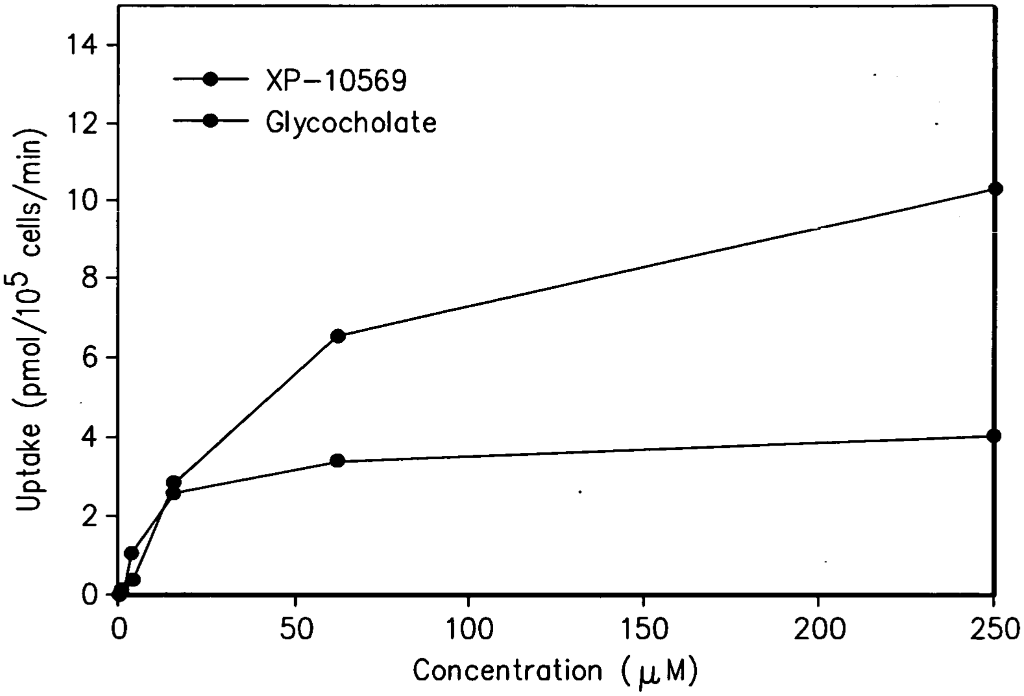
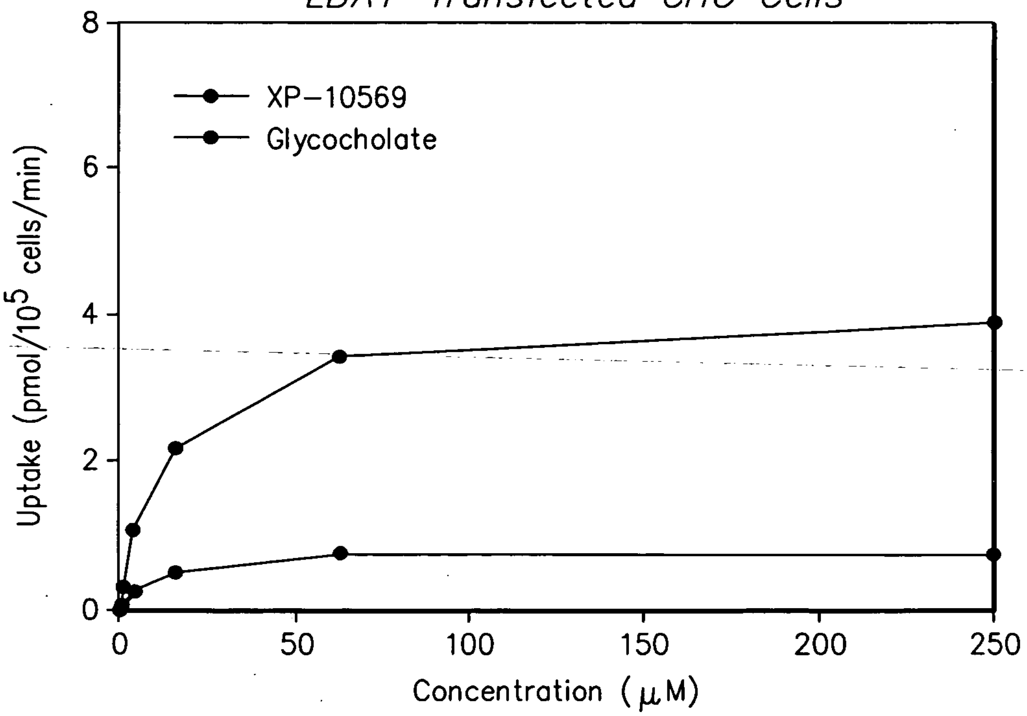


FIG. 10 Uptake of (8) (XP10569) or Glycocholate by LBAT-Transfected CHO Cells



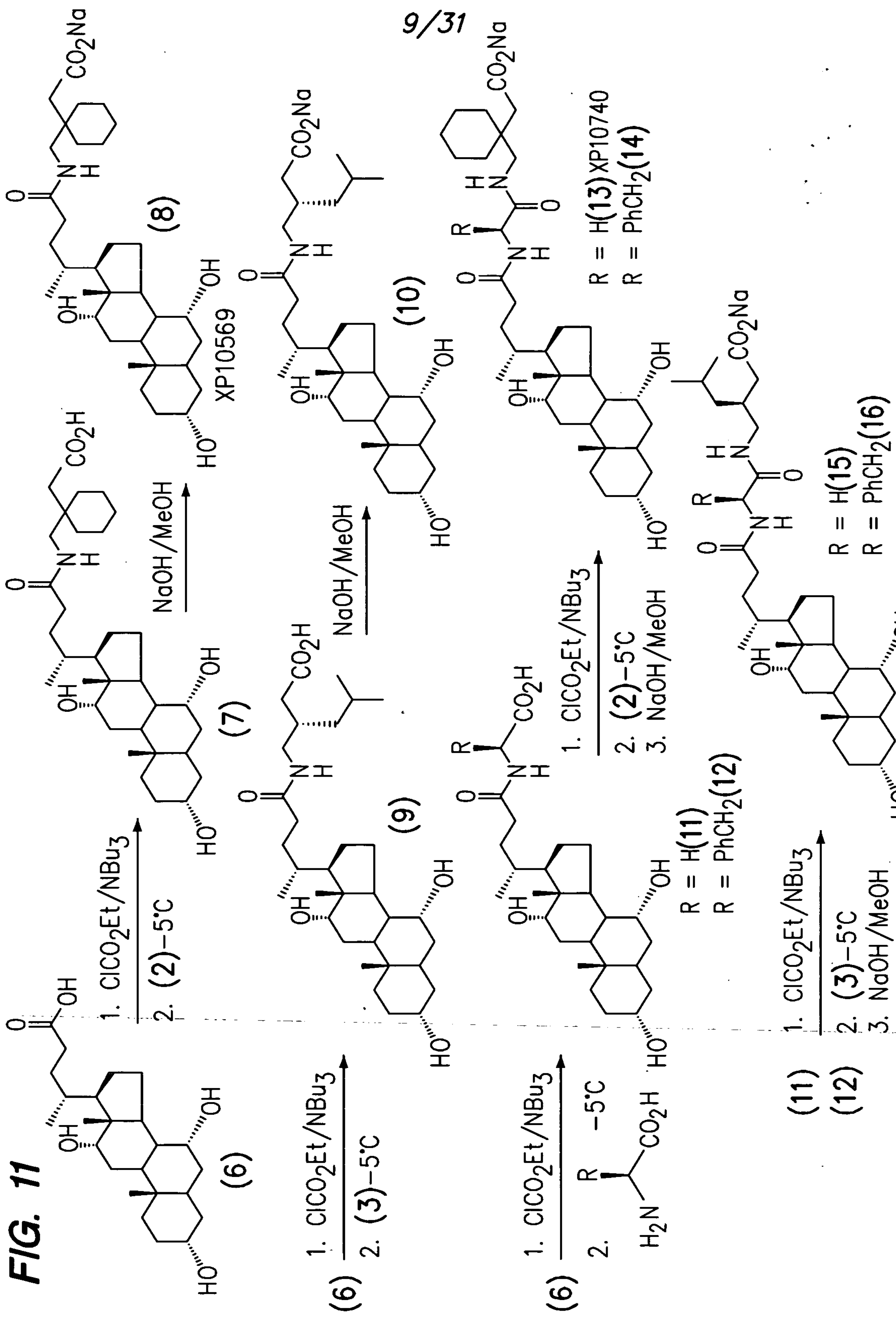

(6)
1. ClCO2Et/NBu3
2. (2)-5°C
(7)
NaOH/MeOH
(8)
XP10569
(6)
1. ClCO2Et/NBu3
2. (3)-5°C
(9)
NaOH/MeOH
(10)
(6)
1. ClCO2Et/NBu3
2. H2N CO2H R -5°C
R = H(11)
R = PhCH2(12)
1. ClCO2Et/NBu3
2. (2)-5°C
3. NaOH/MeOH
R = H(13)XP10740
R = PhCH2(14)
(11)
(12)
1. ClCO2Et/NBu3
2. (3)-5°C
3. NaOH/MeOH
R = H(15)
R = PhCH2(16)

FIG. 11

FIG. 12

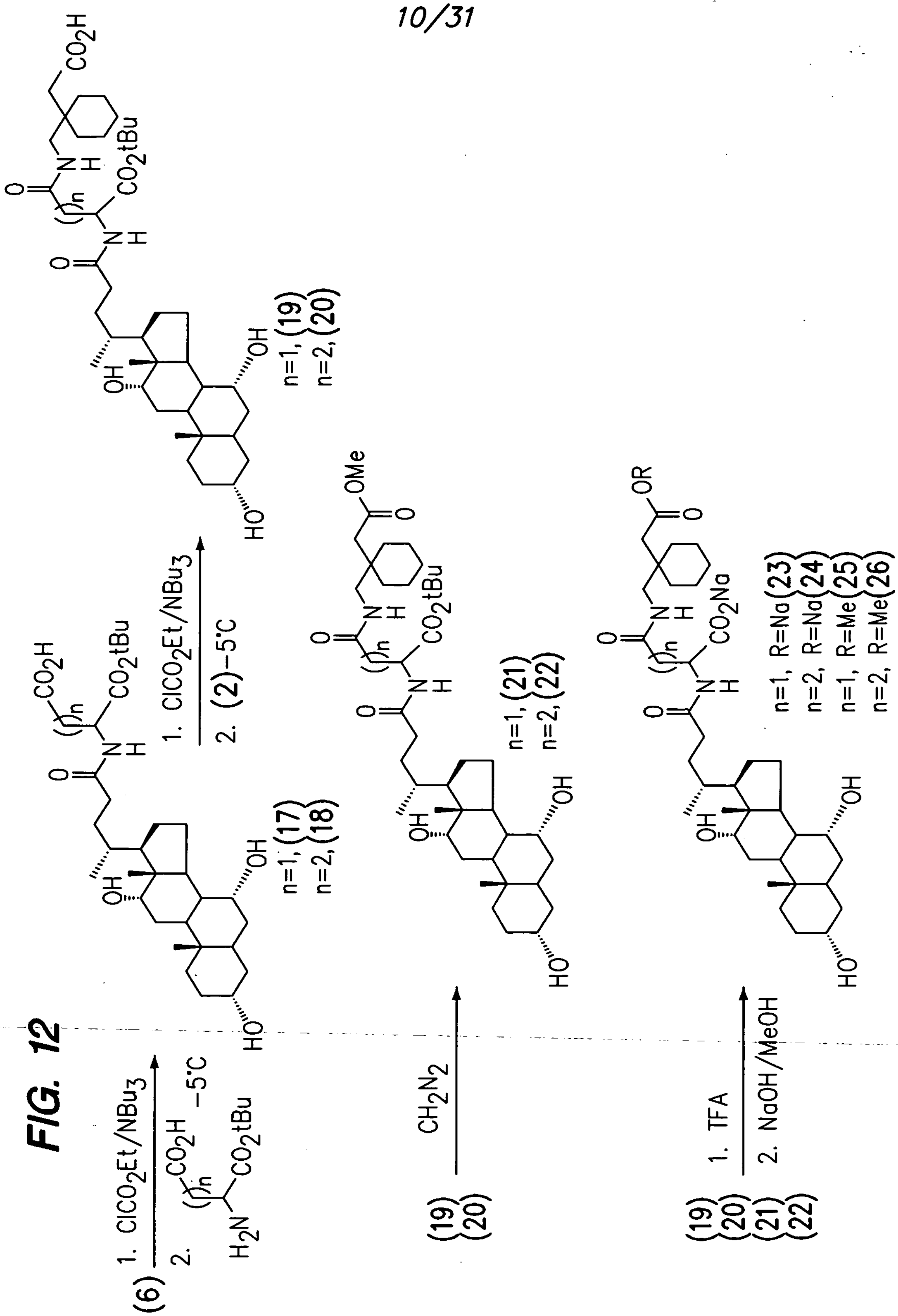

(6)
1. ClCO2Et/NBu3
2. H2N CO2tBu CO2H n
-5°C
n=1, (17)
n=2, (18)
1. ClCO2Et/NBu3
2. (2)-5°C
n=1, (19)
n=2, (20)
(19)
(20)
CH2N2
n=1, (21)
n=2, (22)
(19)
(20)
(21)
(22)
1. TFA
2. NaOH/MeOH
n=1, R=Na (23)
n=2, R=Na (24)
n=1, R=Me (25)
n=2, R=Me (26)

FIG. 13

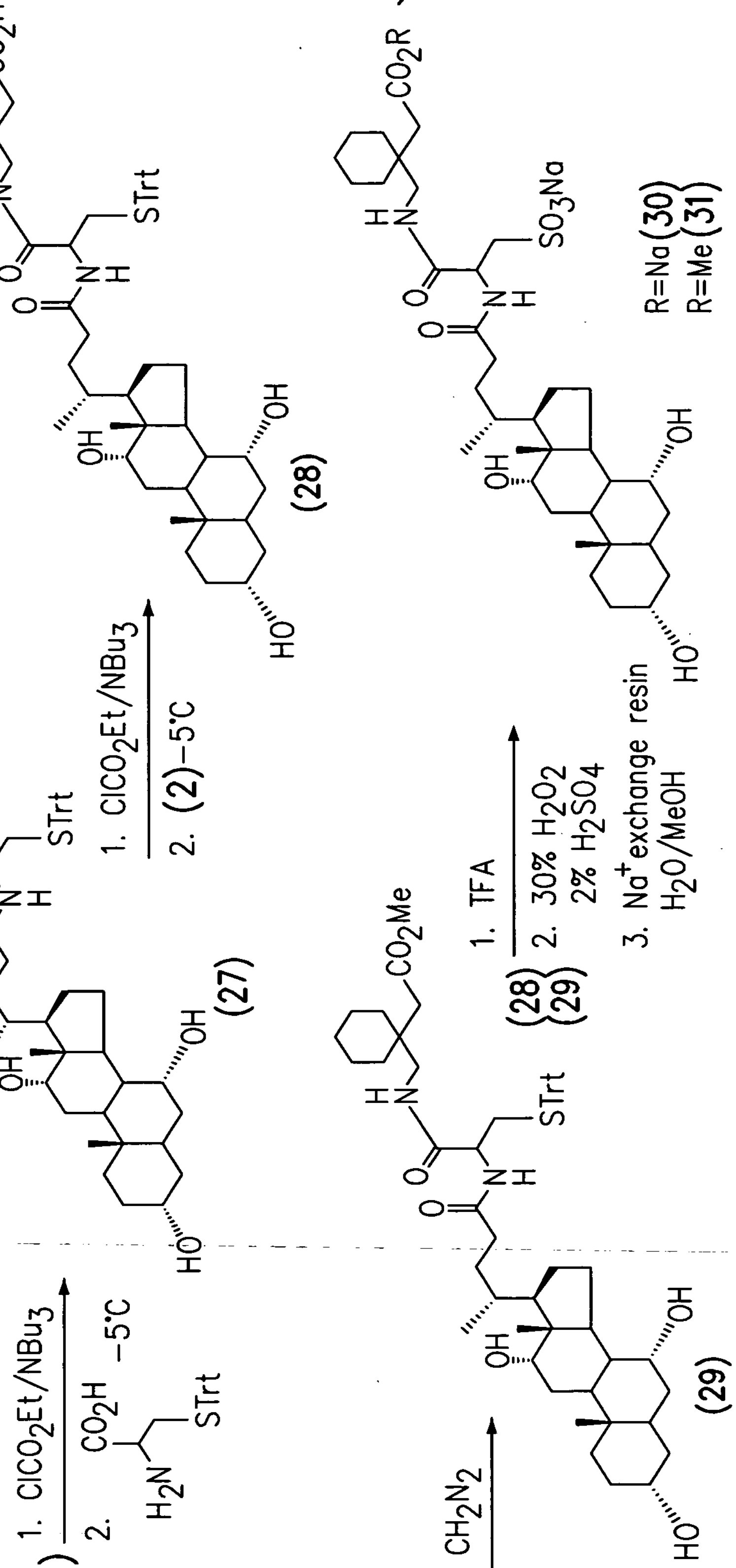

(6)
1. ClCO2Et/NBu3
2. H2N CO2H STrt −5°C
(27)
1. ClCO2Et/NBu3
2. (2)−5°C
(28)
CH2N2
(29)
(28)
(29)
1. TFA
2. 30% H2O2
2% H2SO4
3. Na+exchange resin
H2O/MeOH
R=Na (30)
R=Me (31)

FIG. 14

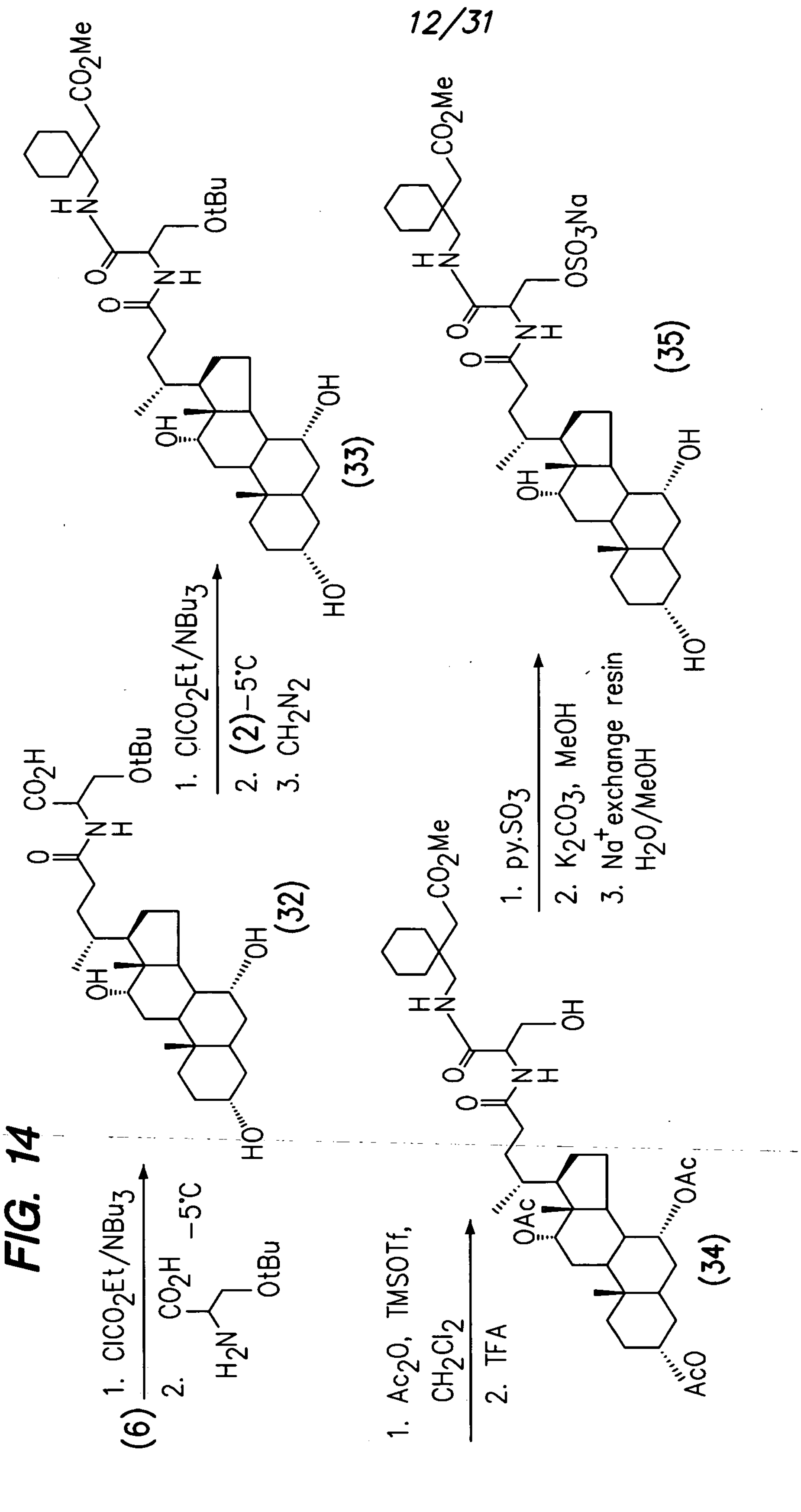

(6)
1. $ClCO_2Et/NBu_3$
2. H_2N CO_2H OtBu −5°C
(32)
1. $ClCO_2Et/NBu_3$
2. (2)−5°C
3. CH_2N_2
(33)
CO_2Me
OtBu
1. Ac_2O, TMSOTf, CH_2Cl_2
2. TFA
(34)
AcO
OAc
1. py.SO_3
2. K_2CO_3, MeOH
3. Na^+exchange resin H_2O/MeOH
(35)
OSO_3Na

FIG. 15

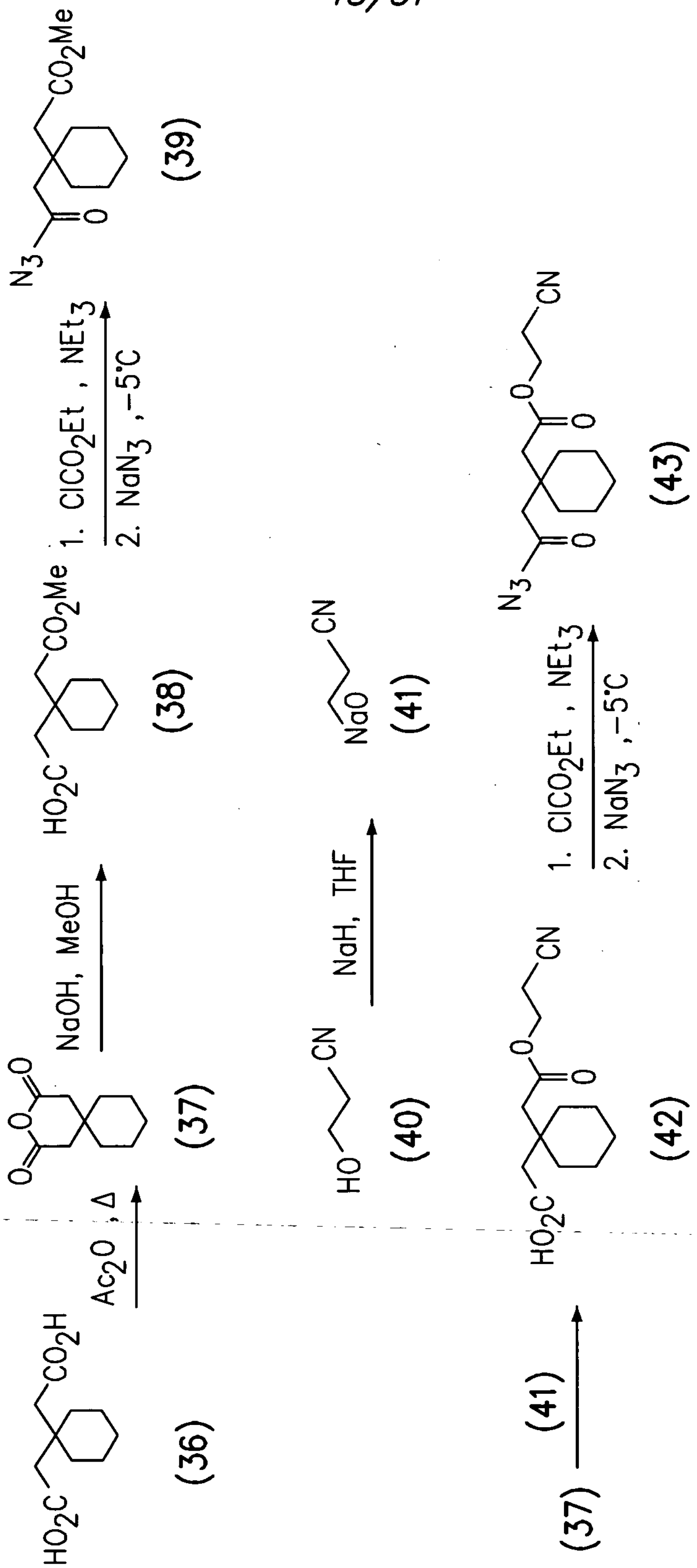

(36)
Ac_2O, Δ
(37)
NaOH, MeOH
(38)
1. $ClCO_2Et$, NEt_3
2. NaN_3, –5°C
(39)
(40)
NaH, THF
(41)
(37)
(41)
(42)
1. $ClCO_2Et$, NEt_3
2. NaN_3, –5°C
(43)

FIG. 16

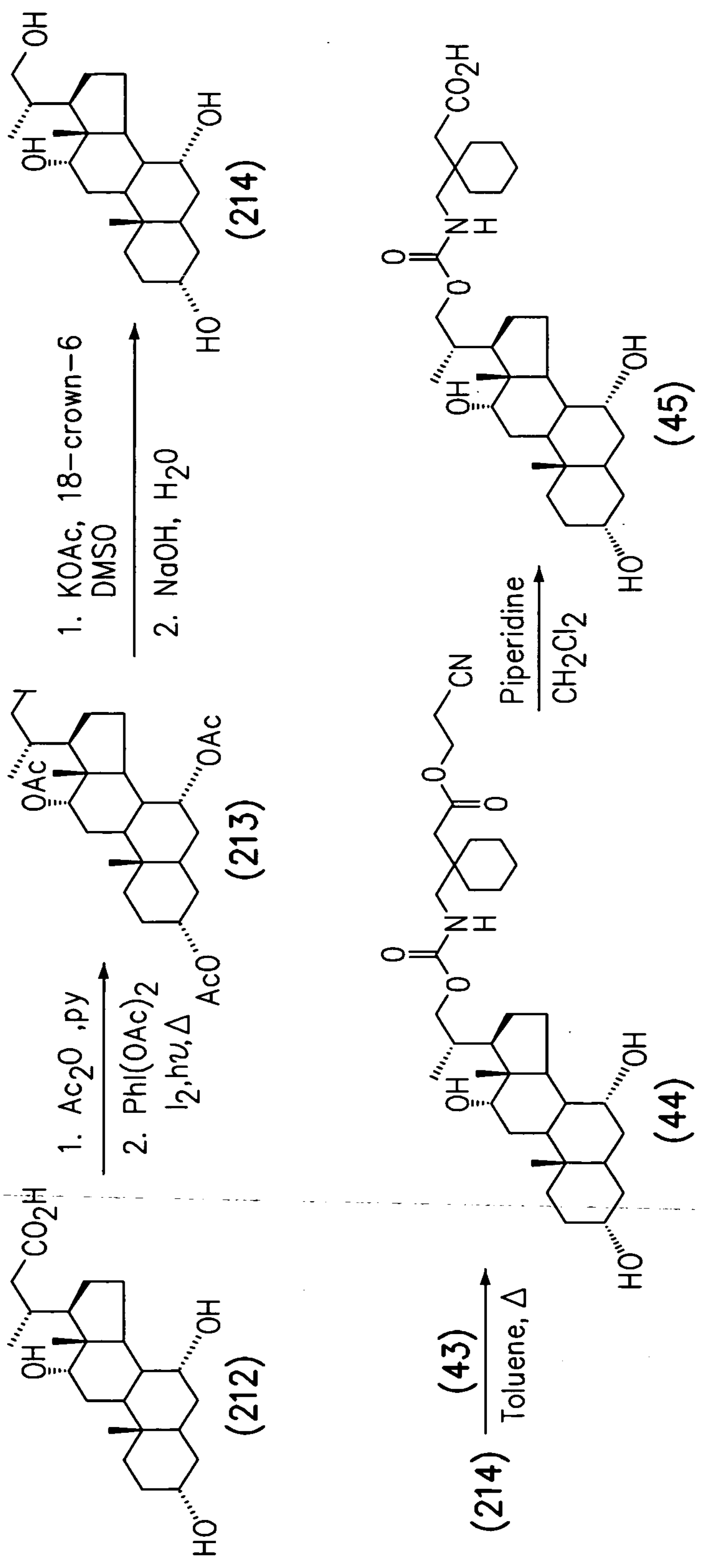

(212)
1. Ac_2O ,py
2. $PhI(OAc)_2$
I_2,hν,Δ
(213)
1. KOAc, 18-crown-6
DMSO
2. NaOH, H_2O
(214)
(214)
(43)
Toluene, Δ
(44)
Piperidine
CH_2Cl_2
(45)

FIG. 17

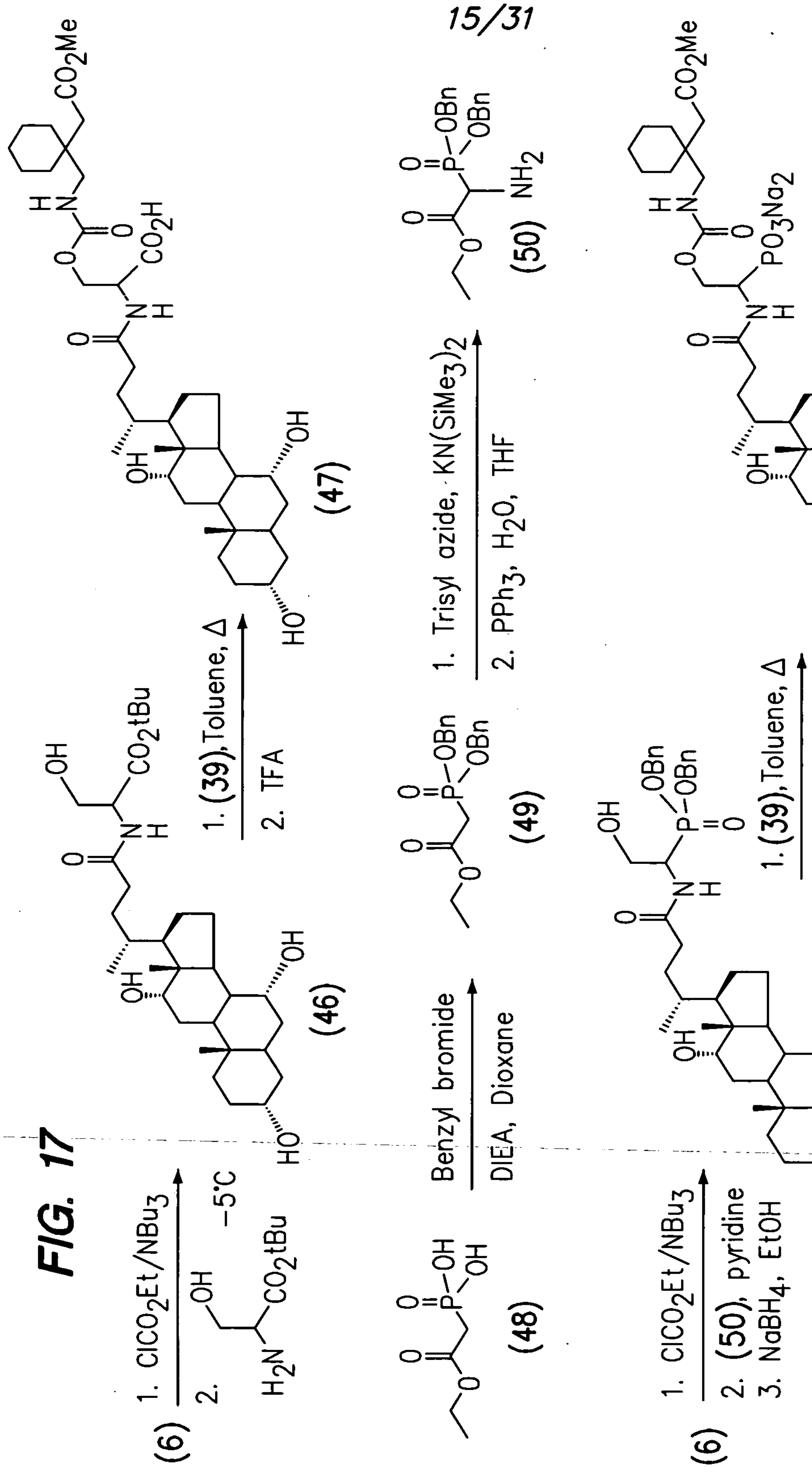

(6)
1. $ClCO_2Et/NBu_3$
2. H_2N–CH(CH_2OH)–CO_2tBu, −5°C
(46)
1. (39), Toluene, Δ
2. TFA
(47)
(48)
Benzyl bromide
DIEA, Dioxane
(49)
1. Trisyl azide, $KN(SiMe_3)_2$
2. PPh_3, H_2O, THF
(50)
(6)
1. $ClCO_2Et/NBu_3$
2. (50), pyridine
3. $NaBH_4$, EtOH
(51)
1. (39), Toluene, Δ
2. H_2, Pd/C
3. Na^+exchange resin $H_2O/MeOH$
(52)

FIG. 18

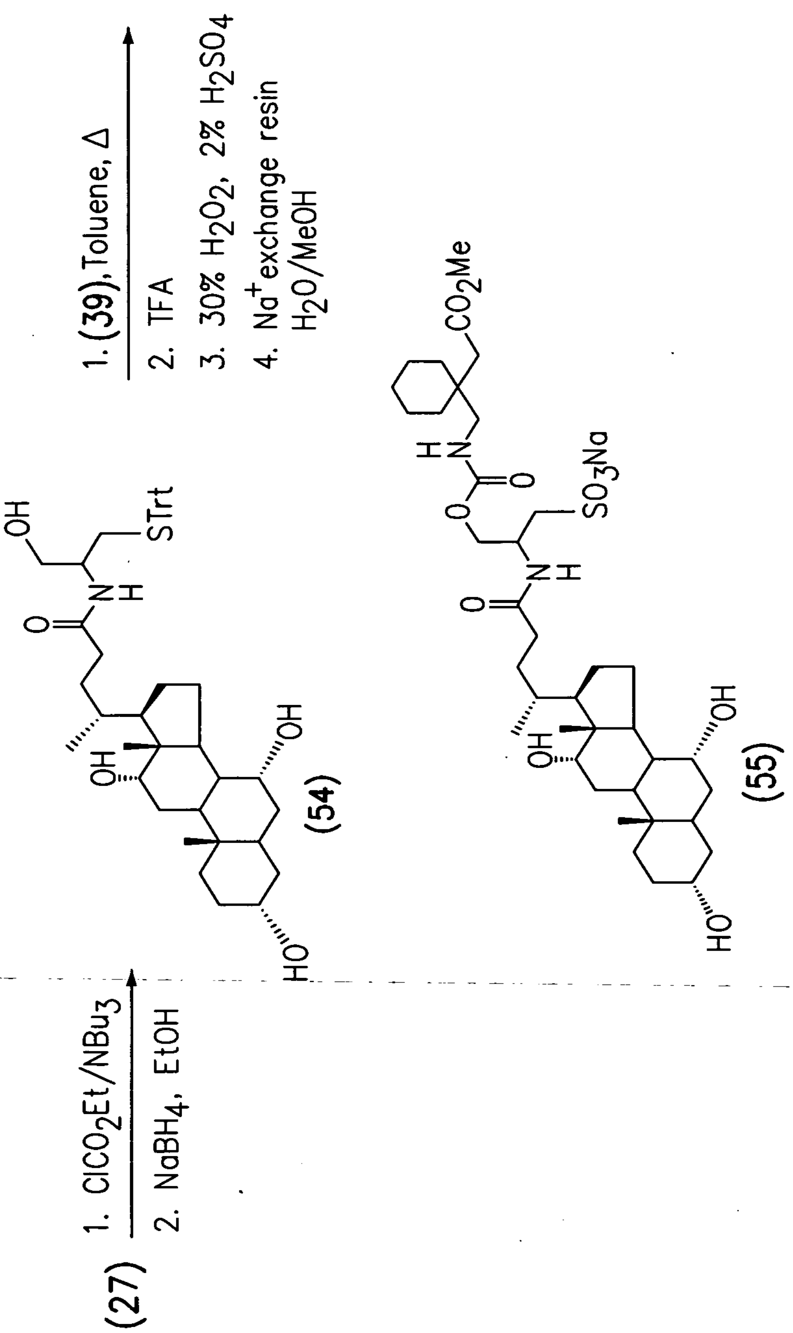
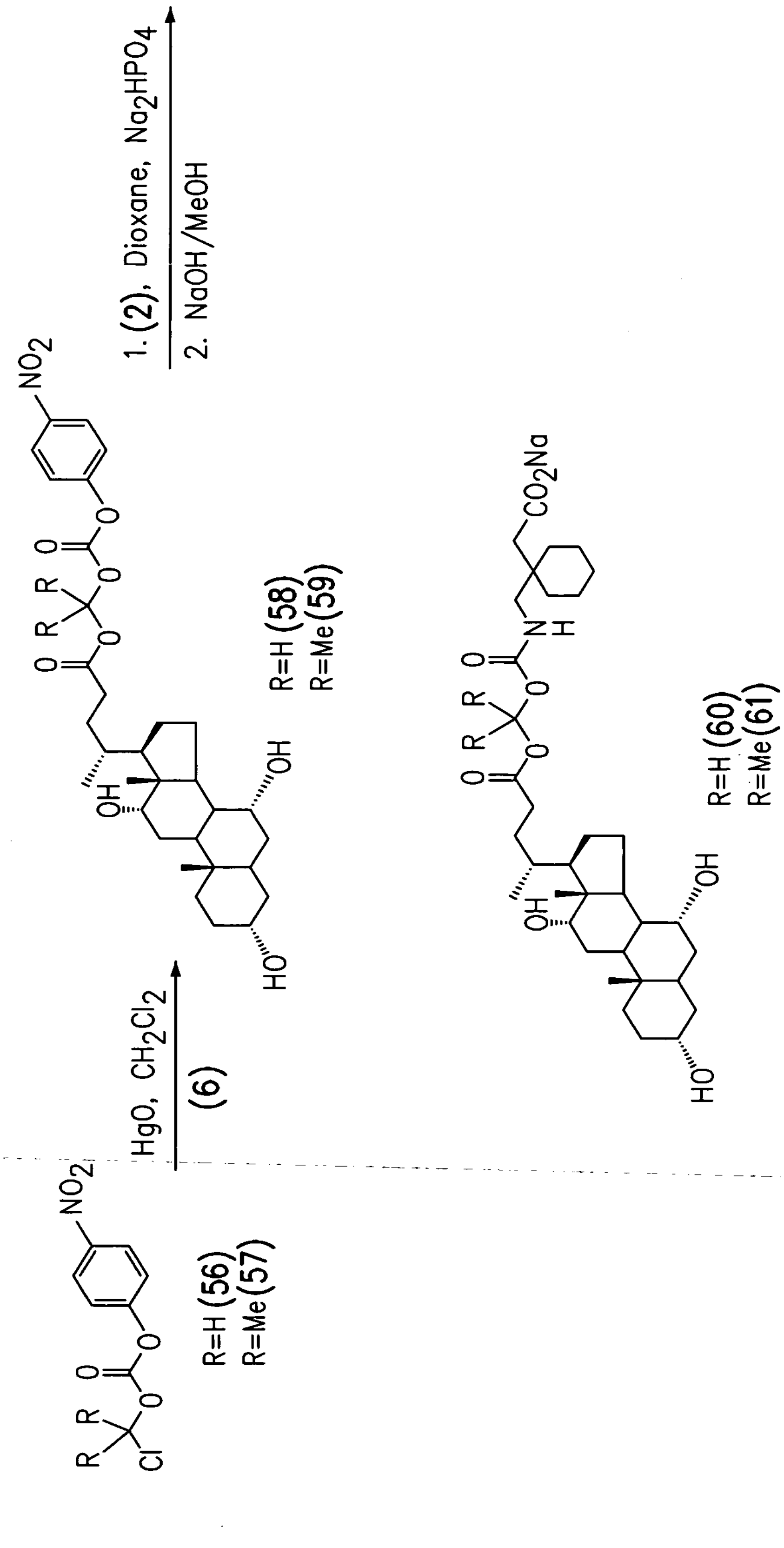

(27)
1. $ClCO_2Et/NBu_3$
2. $NaBH_4$, EtOH
(54)
1. (39), Toluene, Δ
2. TFA
3. 30% H_2O_2, 2% H_2SO_4
4. Na^+exchange resin
$H_2O/MeOH$
(55)

FIG. 19


R=H (56)
R=Me (57)
HgO, CH_2Cl_2
(6)
R=H (58)
R=Me (59)
1. (2), Dioxane, Na_2HPO_4
2. NaOH/MeOH
R=H (60)
R=Me (61)

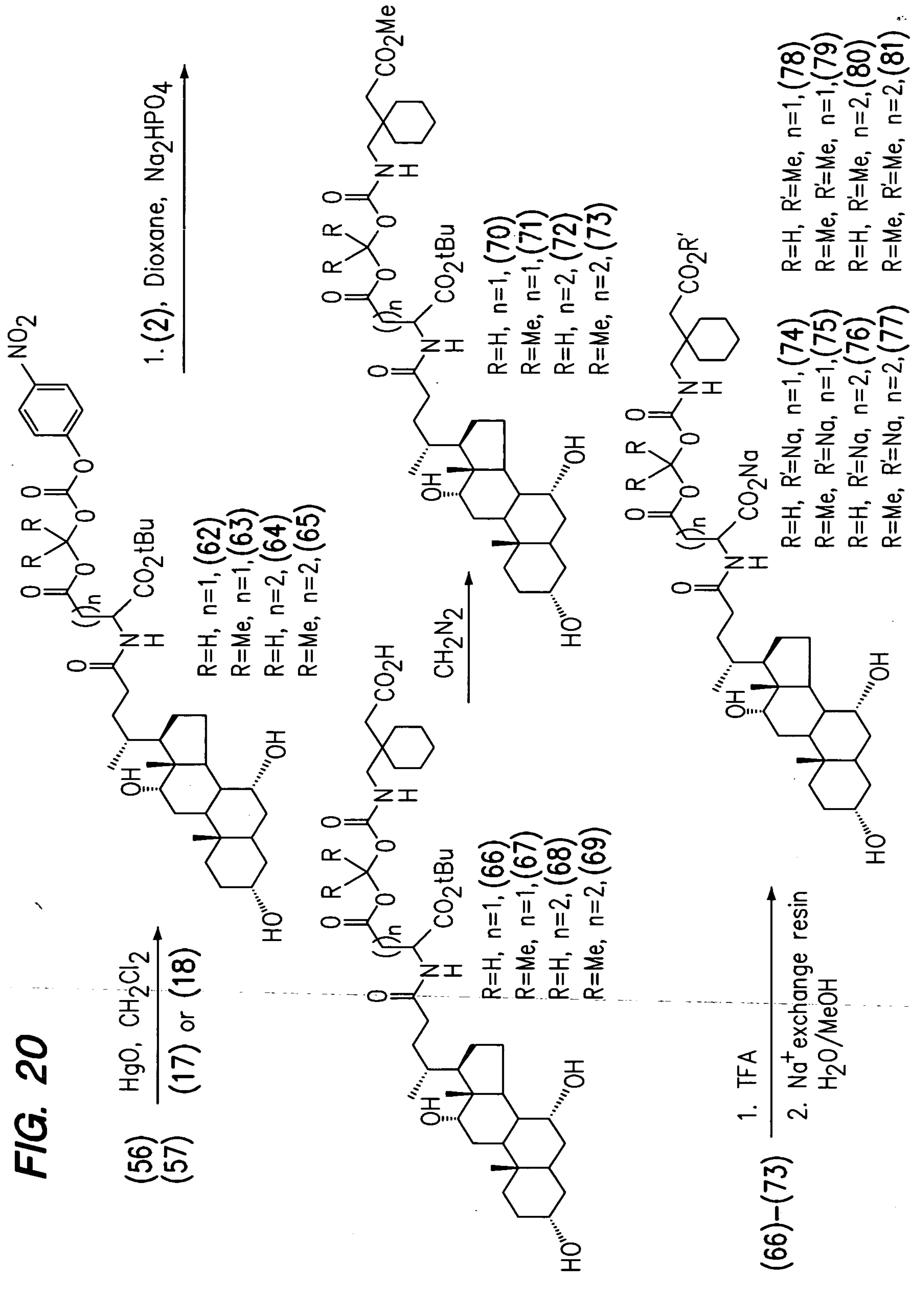


FIG. 20
(56)
(57)
HgO, CH_2Cl_2
(17) or (18)
NO_2
CO_2tBu
R=H, n=1, (62)
R=Me, n=1, (63)
R=H, n=2, (64)
R=Me, n=2, (65)
1. (2), Dioxane, Na_2HPO_4
CO_2H
R=H, n=1, (66)
R=Me, n=1, (67)
R=H, n=2, (68)
R=Me, n=2, (69)
CH_2N_2
CO_2Me
R=H, n=1, (70)
R=Me, n=1, (71)
R=H, n=2, (72)
R=Me, n=2, (73)
(66)–(73)
1. TFA
2. Na^+ exchange resin H_2O/MeOH
CO_2Na
CO_2R'
R=H, R'=Na, n=1, (74)
R=Me, R'=Na, n=1, (75)
R=H, R'=Na, n=2, (76)
R=Me, R'=Na, n=2, (77)
R=H, R'=Me, n=1, (78)
R=Me, R'=Me, n=1, (79)
R=H, R'=Me, n=2, (80)
R=Me, R'=Me, n=2, (81)

FIG. 21

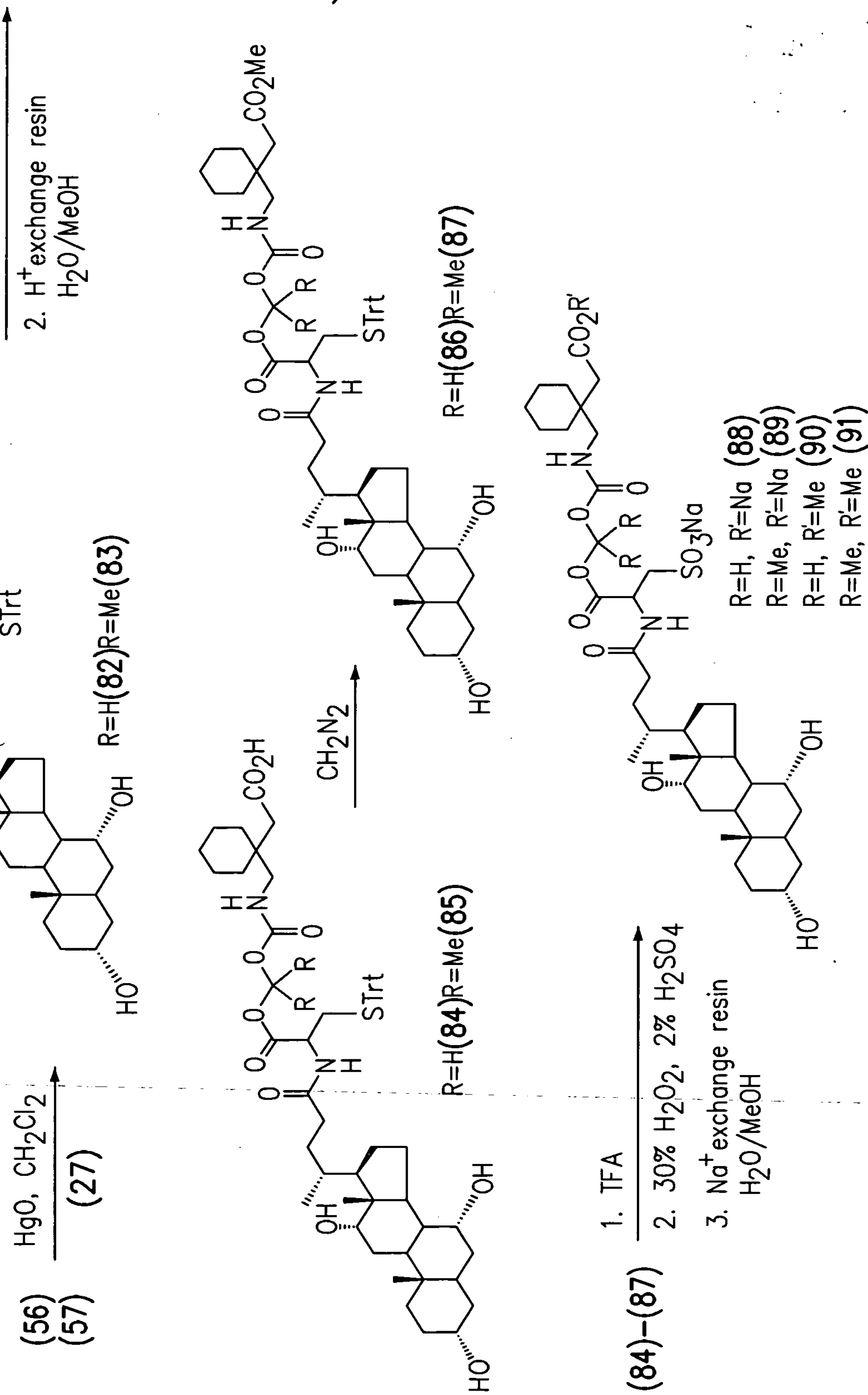
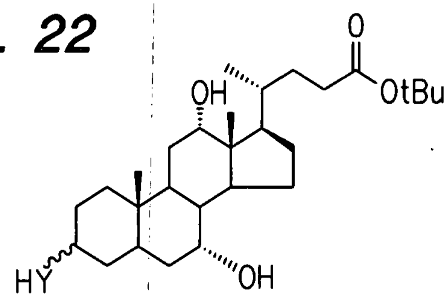
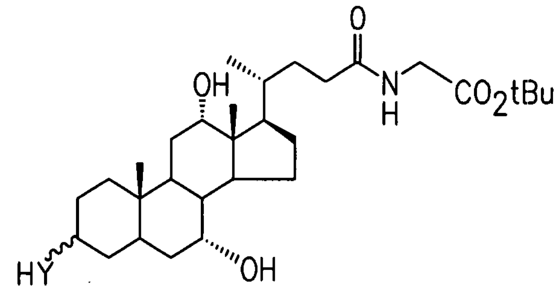

(56)
(57)
HgO, CH_2Cl_2
(27)
R=H(82)R=Me(83)
1. (2), Dioxane, Na_2HPO_4
2. H^+exchange resin
H_2O/MeOH
R=H(84)R=Me(85)
CH_2N_2
R=H(86)R=Me(87)
(84)–(87)
1. TFA
2. 30% H_2O_2, 2% H_2SO_4
3. Na^+exchange resin
H_2O/MeOH
R=H, R'=Na (88)
R=Me, R'=Na (89)
R=H, R'=Me (90)
R=Me, R'=Me (91)

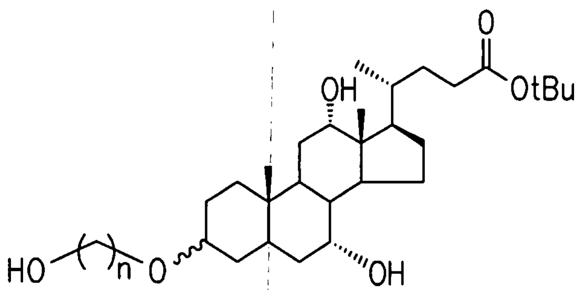
FIG. 22



Y=3α-O (92)
Y=3β-O (93)
Y=3α-NH (94)
Y=3β-NH (95)

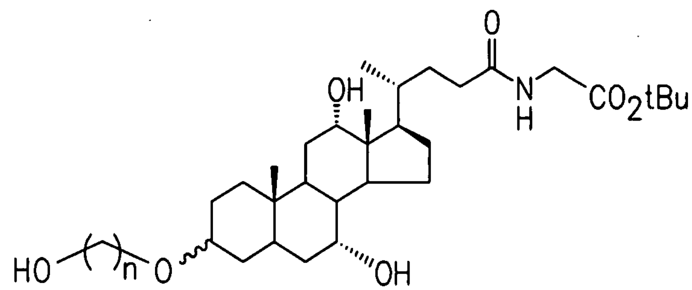


Y=3α-O (96)
Y=3β-O (97)
Y=3α-NH (98)
Y=3β-NH (99)



n=1-5

3α-O (100)
3β-O (101)

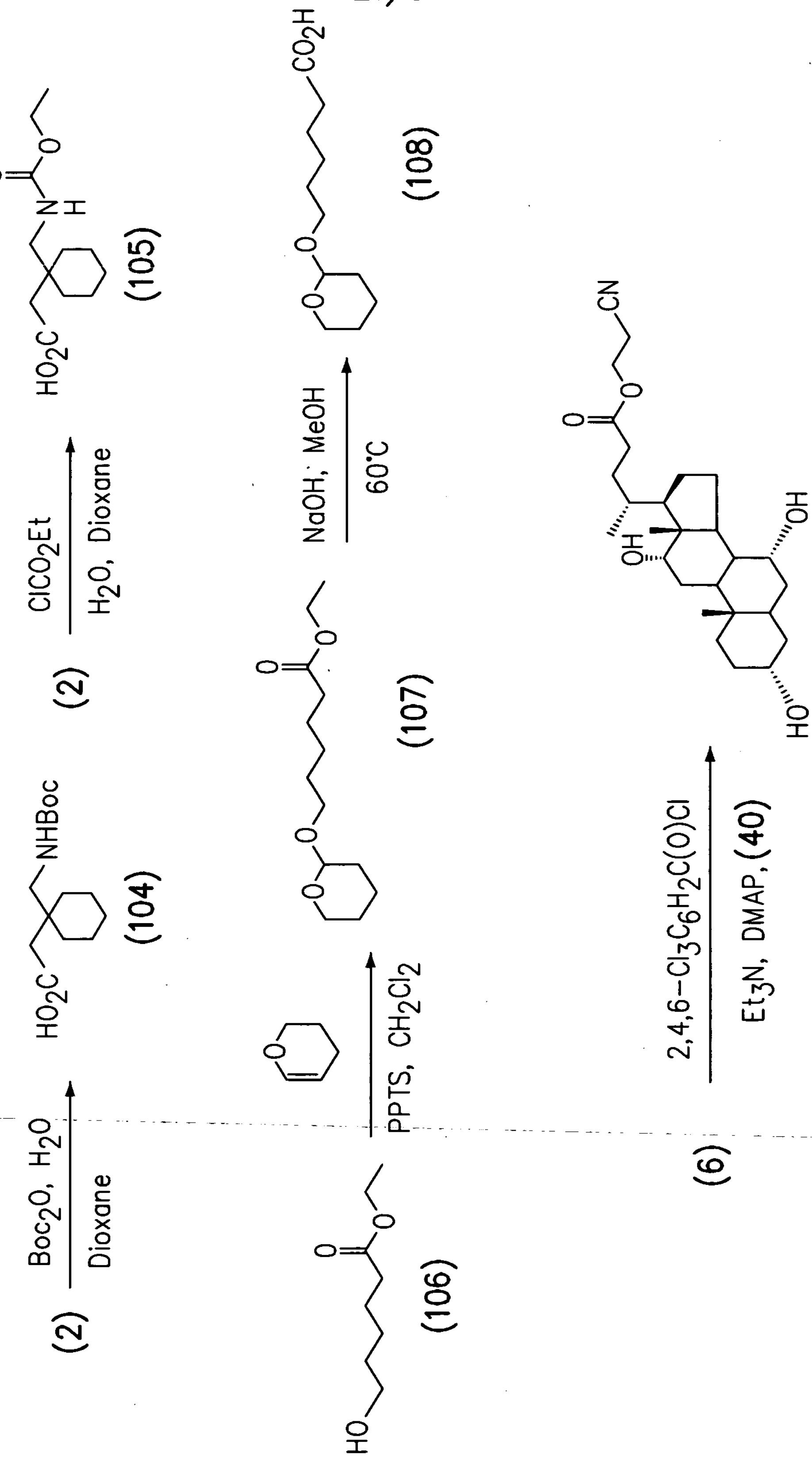


n=1-5

3α-O (102)
3β-O (103)

Compounds (92)-(103) prepared following methods described in co-pending application "Bile Acid-Derived Compounds for Enhancing Oral Absorption and Systemic Bioavailability of Drugs" assigned to XenoPort, Inc.

FIG. 23


(2)
Boc2O, H2O
Dioxane
HO2C
NHBoc
(104)
(2)
ClCO2Et
H2O, Dioxane
HO2C
N
H
O
O
(105)
HO
O
O
(106)
PPTS, CH2Cl2
O
O
O
O
O
(107)
NaOH; MeOH
60°C
O
O
CO2H
(108)
(6)
2,4,6-Cl3C6H2C(O)Cl
Et3N, DMAP, (40)
HO
OH
OH
O
O
CN
(109)

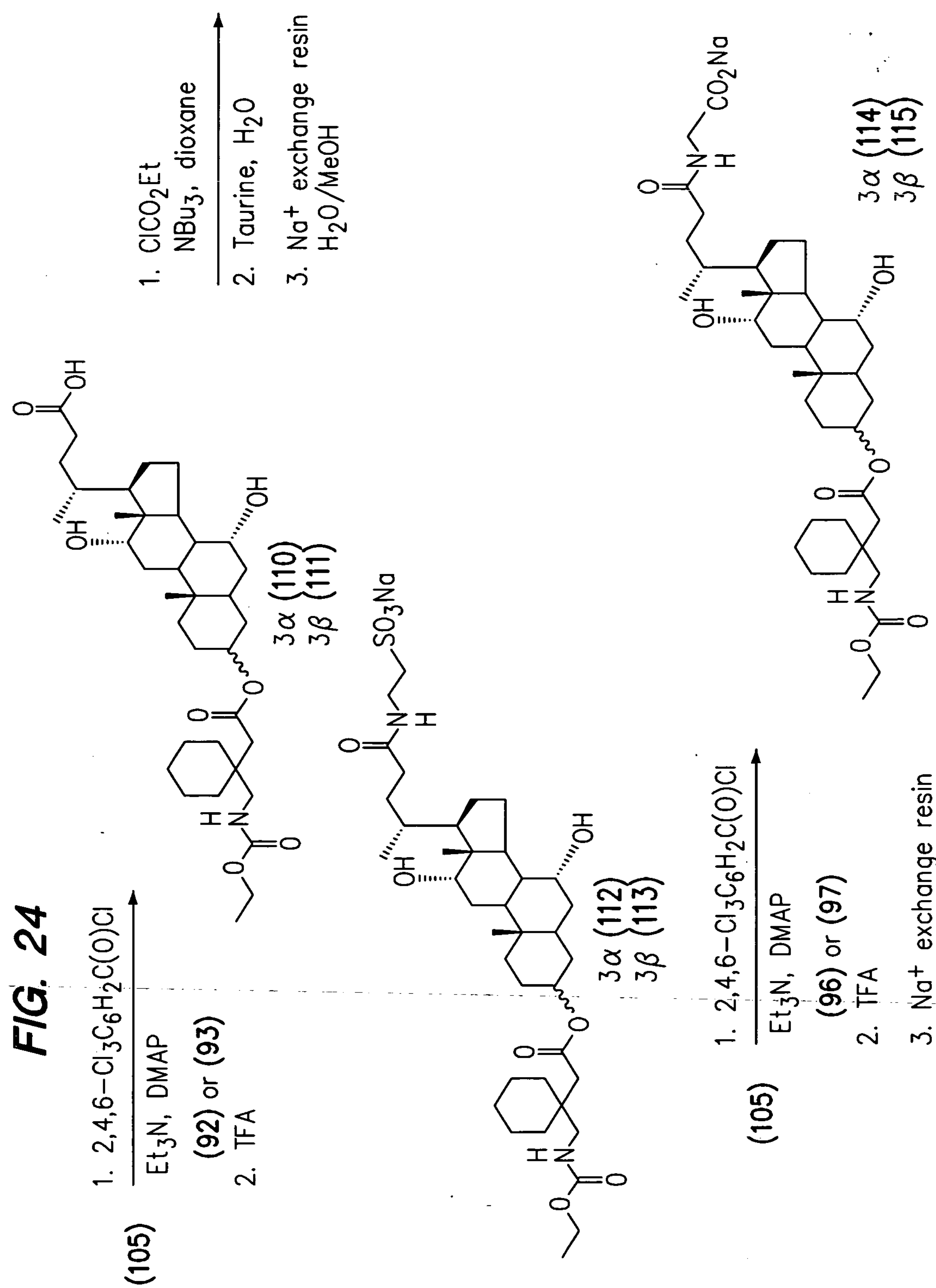
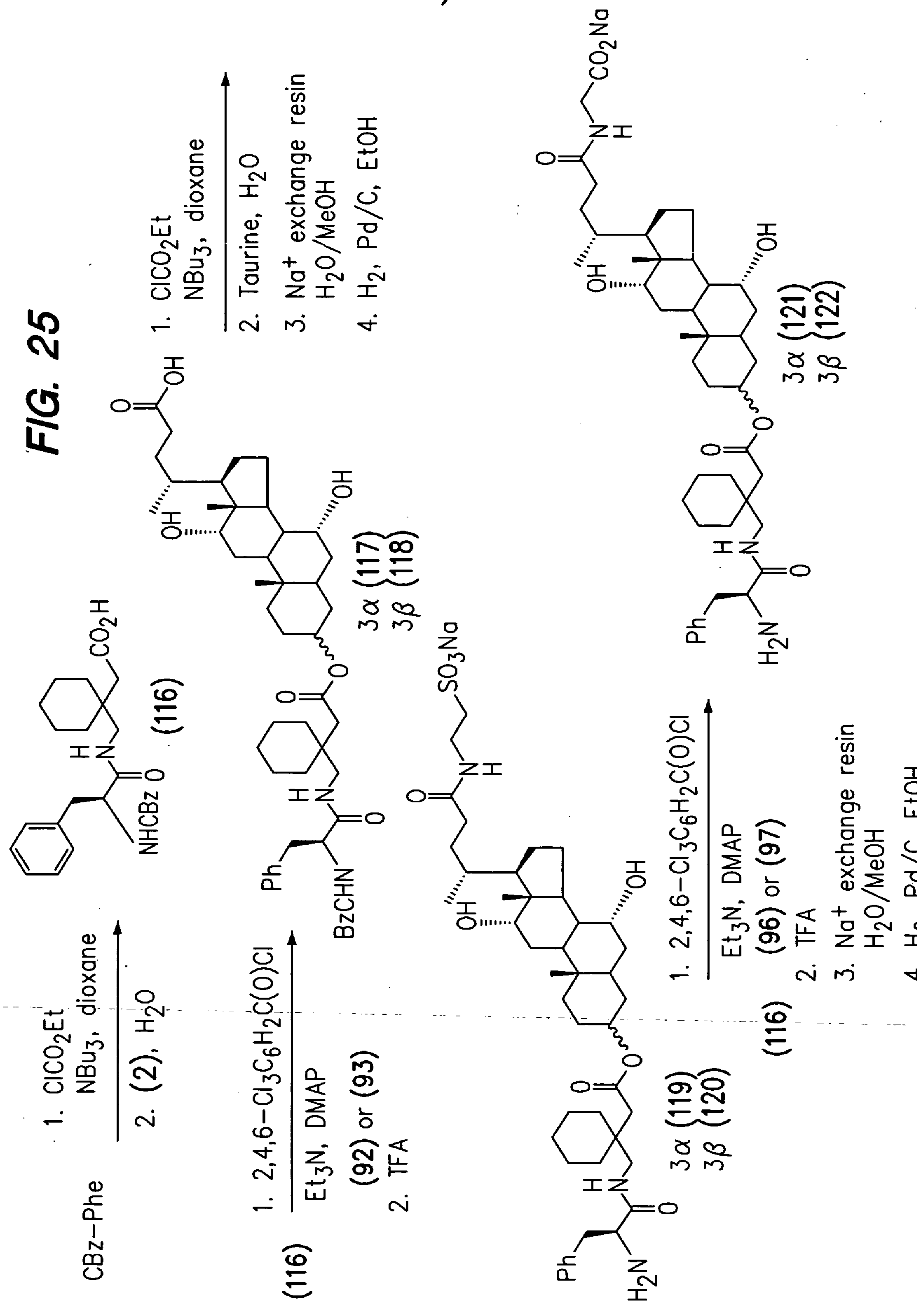

(105)
1. 2,4,6−$Cl_3C_6H_2C(O)Cl$
Et_3N, DMAP
(92) or (93)
2. TFA
3α (110)
3β (111)
1. $ClCO_2Et$
NBu_3, dioxane
2. Taurine, H_2O
3. Na^+ exchange resin
H_2O/MeOH
SO_3Na
3α (112)
3β (113)
(105)
1. 2,4,6−$Cl_3C_6H_2C(O)Cl$
Et_3N, DMAP
(96) or (97)
2. TFA
3. Na^+ exchange resin
H_2O/MeOH
CO_2Na
3α (114)
3β (115)

FIG. 24

FIG. 25


CBz–Phe
1. $ClCO_2Et$ NBu_3, dioxane
2. (2), H_2O
NHCBz
CO_2H
(116)
(116)
1. 2,4,6–$Cl_3C_6H_2C(O)Cl$ Et_3N, DMAP (92) or (93)
2. TFA
BzCHN
Ph
OH
OH
OH
3α (117)
3β (118)
1. $ClCO_2Et$ NBu_3, dioxane
2. Taurine, H_2O
3. Na^+ exchange resin H_2O/MeOH
4. H_2, Pd/C, EtOH
SO_3Na
H_2N
3α (119)
3β (120)
(116)
1. 2,4,6–$Cl_3C_6H_2C(O)Cl$ Et_3N, DMAP (96) or (97)
2. TFA
3. Na^+ exchange resin H_2O/MeOH
4. H_2, Pd/C, EtOH
CO_2Na
3α (121)
3β (122)

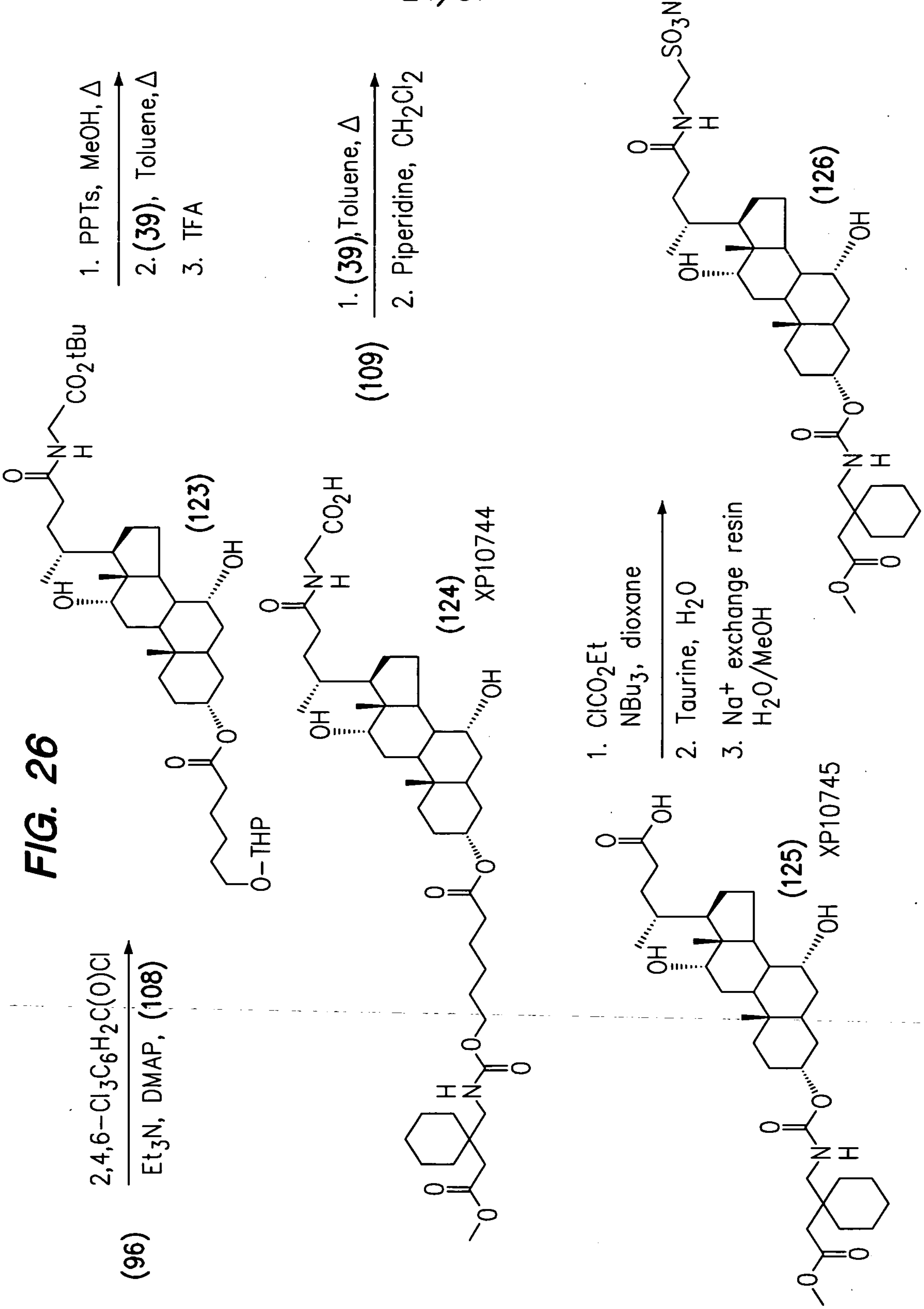
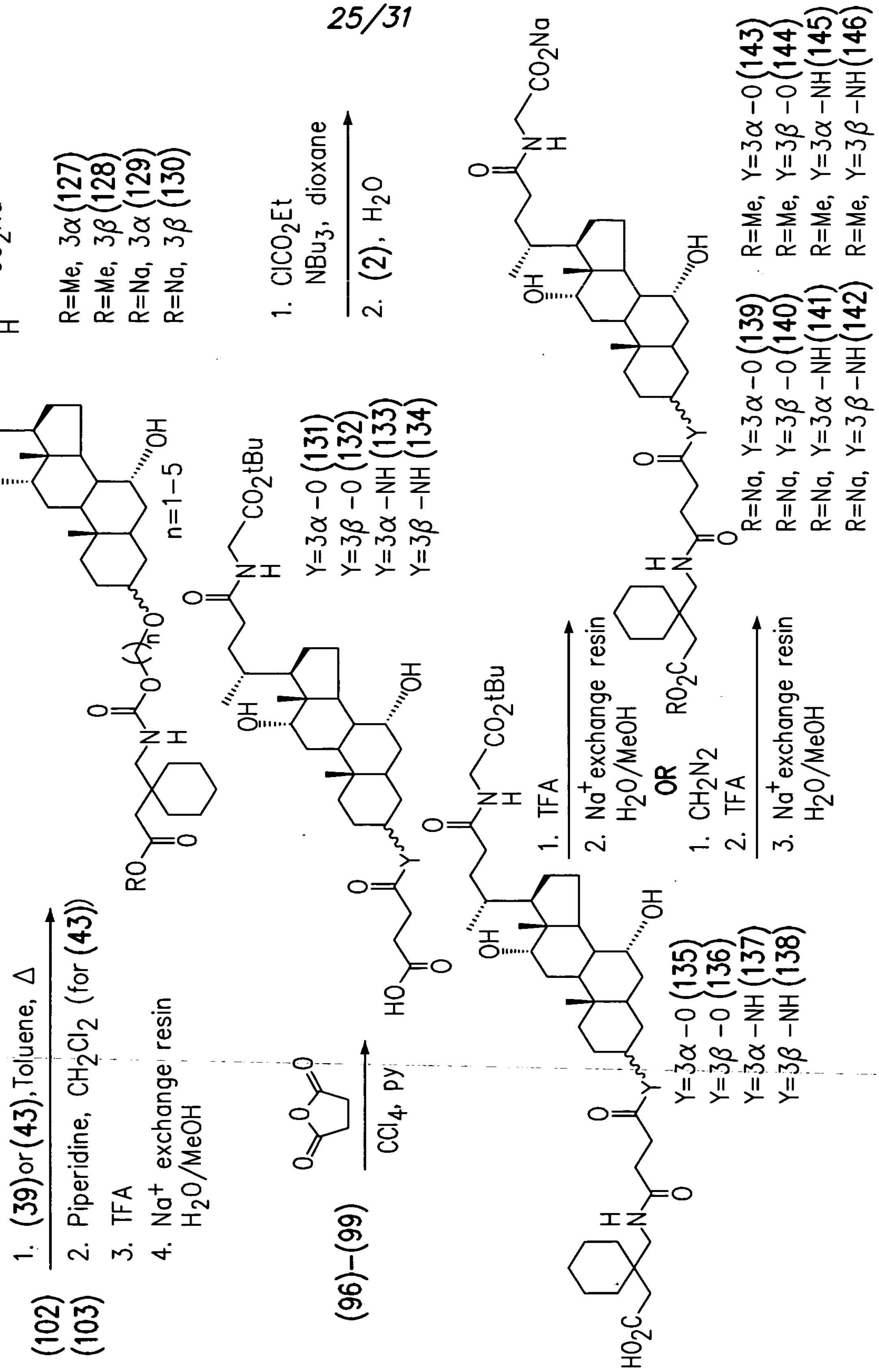

(96)
2,4,6–Cl3C6H2C(O)Cl
Et3N, DMAP, (108)
(123)
1. PPTs, MeOH, Δ
2. (39), Toluene, Δ
3. TFA
(124)
XP10744
(109)
1. (39), Toluene, Δ
2. Piperidine, CH2Cl2
1. ClCO2Et NBu3, dioxane
2. Taurine, H2O
3. Na+ exchange resin H2O/MeOH
(125)
XP10745
(126)

FIG. 26

FIG. 27


(102)
(103)
1. (39) or (43), Toluene, Δ
2. Piperidine, CH2Cl2 (for (43))
3. TFA
4. Na+ exchange resin H2O/MeOH
RO
O
N
H
n
OH
OH
CO2Na
R=Me, 3α (127)
R=Me, 3β (128)
R=Na, 3α (129)
R=Na, 3β (130)
n=1–5
(96)–(99)
CCl4, py
HO
Y
CO2tBu
Y=3α –O (131)
Y=3β –O (132)
Y=3α –NH (133)
Y=3β –NH (134)
1. ClCO2Et NBu3, dioxane
2. (2), H2O
HO2C
Y=3α –O (135)
Y=3β –O (136)
Y=3α –NH (137)
Y=3β –NH (138)
1. TFA
2. Na+ exchange resin H2O/MeOH
OR
1. CH2N2
2. TFA
3. Na+ exchange resin H2O/MeOH
RO2C
R=Na, Y=3α –O (139)
R=Na, Y=3β –O (140)
R=Na, Y=3α –NH (141)
R=Na, Y=3β –NH (142)
R=Me, Y=3α –O (143)
R=Me, Y=3β –O (144)
R=Me, Y=3α –NH (145)
R=Me, Y=3β –NH (146)

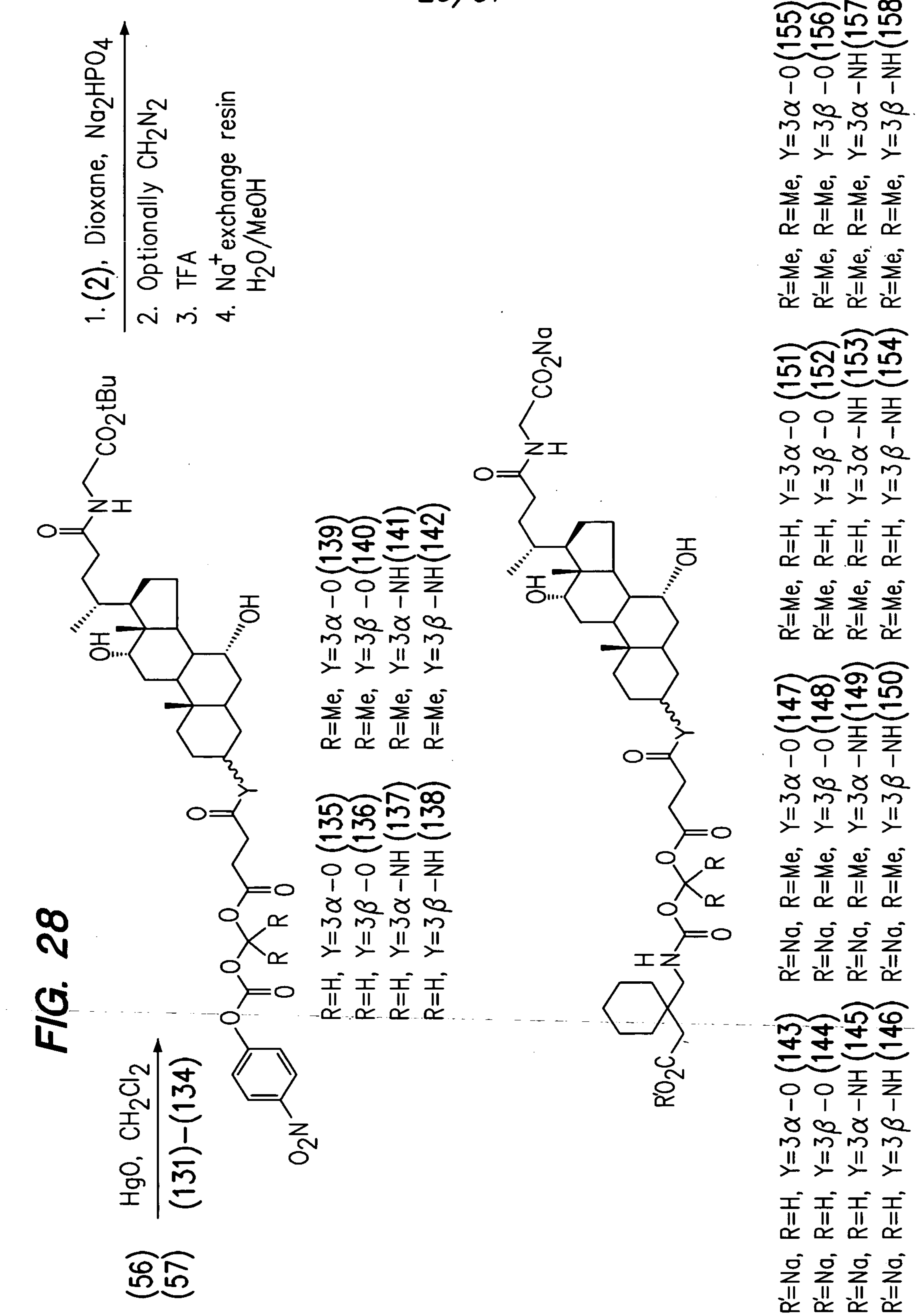
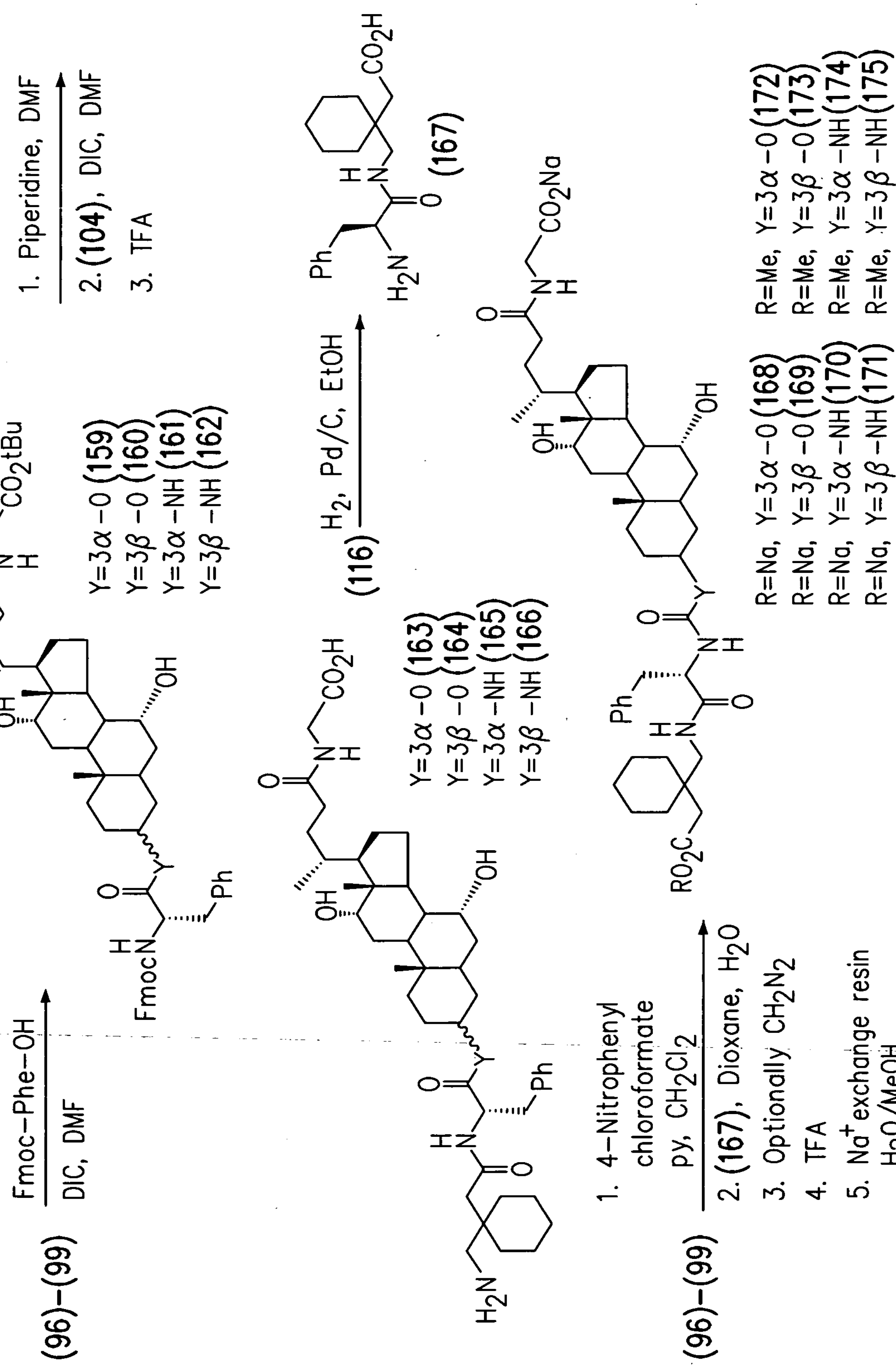

(56)
(57)
HgO, CH2Cl2
(131)-(134)
O2N
R=H, Y=3α-O (135)
R=H, Y=3β-O (136)
R=H, Y=3α-NH (137)
R=H, Y=3β-NH (138)
R=Me, Y=3α-O (139)
R=Me, Y=3β-O (140)
R=Me, Y=3α-NH (141)
R=Me, Y=3β-NH (142)
CO2tBu
1. (2), Dioxane, Na2HPO4
2. Optionally CH2N2
3. TFA
4. Na+ exchange resin
H2O/MeOH
R'O2C
CO2Na
R'=Na, R=H, Y=3α-O (143)
R'=Na, R=H, Y=3β-O (144)
R'=Na, R=H, Y=3α-NH (145)
R'=Na, R=H, Y=3β-NH (146)
R'=Na, R=Me, Y=3α-O (147)
R'=Na, R=Me, Y=3β-O (148)
R'=Na, R=Me, Y=3α-NH (149)
R'=Na, R=Me, Y=3β-NH (150)
R'=Me, R=H, Y=3α-O (151)
R'=Me, R=H, Y=3β-O (152)
R'=Me, R=H, Y=3α-NH (153)
R'=Me, R=H, Y=3β-NH (154)
R'=Me, R=Me, Y=3α-O (155)
R'=Me, R=Me, Y=3β-O (156)
R'=Me, R=Me, Y=3α-NH (157)
R'=Me, R=Me, Y=3β-NH (158)

FIG. 28

FIG. 29


(96)–(99)
Fmoc–Phe–OH
DIC, DMF
FmocN
Ph
OH
CO2tBu
Y=3α –O (159)
Y=3β –O (160)
Y=3α –NH (161)
Y=3β –NH (162)
1. Piperidine, DMF
2. (104), DIC, DMF
3. TFA
H2N
CO2H
Y=3α –O (163)
Y=3β –O (164)
Y=3α –NH (165)
Y=3β –NH (166)
(116)
H2, Pd/C, EtOH
(167)
1. 4–Nitrophenyl chloroformate py, CH2Cl2
2. (167), Dioxane, H2O
3. Optionally CH2N2
4. TFA
5. Na+ exchange resin H2O/MeOH
RO2C
CO2Na
R=Na, Y=3α –O (168)
R=Na, Y=3β –O (169)
R=Na, Y=3α –NH (170)
R=Na, Y=3β –NH (171)
R=Me, Y=3α –O (172)
R=Me, Y=3β –O (173)
R=Me, Y=3α –NH (174)
R=Me, Y=3β –NH (175)

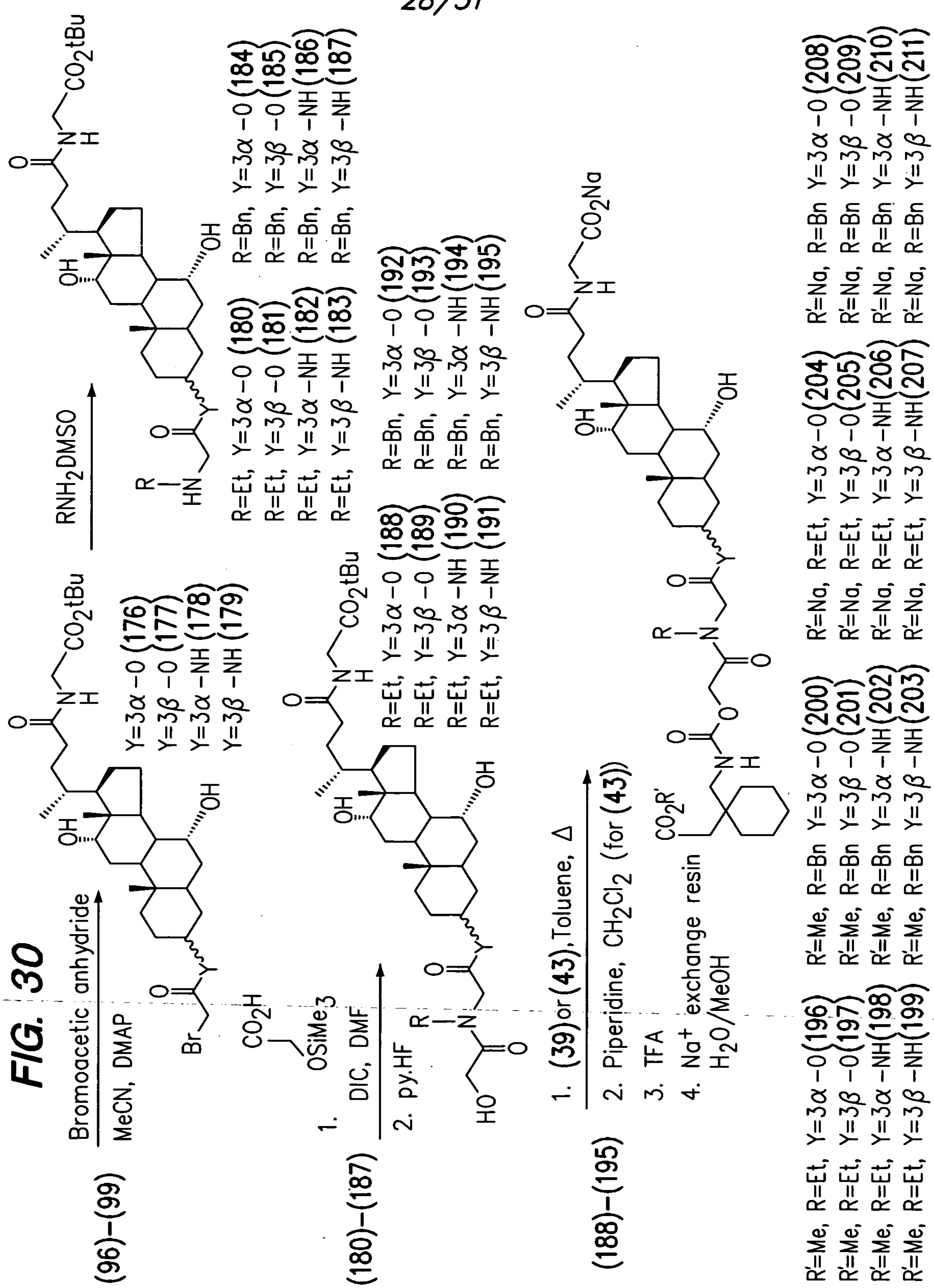

(96)–(99)
Bromoacetic anhydride
MeCN, DMAP
Y=3α–O (176)
Y=3β–O (177)
Y=3α–NH (178)
Y=3β–NH (179)
RNH2DMSO
R=Et, Y=3α–O (180) R=Bn, Y=3α–O (184)
R=Et, Y=3β–O (181) R=Bn, Y=3β–O (185)
R=Et, Y=3α–NH (182) R=Bn, Y=3α–NH (186)
R=Et, Y=3β–NH (183) R=Bn, Y=3β–NH (187)
(180)–(187)
1. CO2H / OSiMe3, DIC, DMF
2. py.HF
R=Et, Y=3α–O (188) R=Bn, Y=3α–O (192)
R=Et, Y=3β–O (189) R=Bn, Y=3β–O (193)
R=Et, Y=3α–NH (190) R=Bn, Y=3α–NH (194)
R=Et, Y=3β–NH (191) R=Bn, Y=3β–NH (195)
(188)–(195)
1. (39) or (43), Toluene, Δ
2. Piperidine, CH2Cl2 (for (43))
3. TFA
4. Na+ exchange resin H2O/MeOH
R′=Me, R=Et, Y=3α–O (196) R′=Me, R=Bn Y=3α–O (200) R′=Na, R=Et, Y=3α–O (204) R′=Na, R=Bn Y=3α–O (208)
R′=Me, R=Et, Y=3β–O (197) R′=Me, R=Bn Y=3β–O (201) R′=Na, R=Et, Y=3β–O (205) R′=Na, R=Bn Y=3β–O (209)
R′=Me, R=Et, Y=3α–NH (198) R′=Me, R=Bn Y=3α–NH (202) R′=Na, R=Et, Y=3α–NH (206) R′=Na, R=Bn Y=3α–NH (210)
R′=Me, R=Et, Y=3β–NH (199) R′=Me, R=Bn Y=3β–NH (203) R′=Na, R=Et, Y=3β–NH (207) R′=Na, R=Bn Y=3β–NH (211)

FIG. 30

FIG. 31

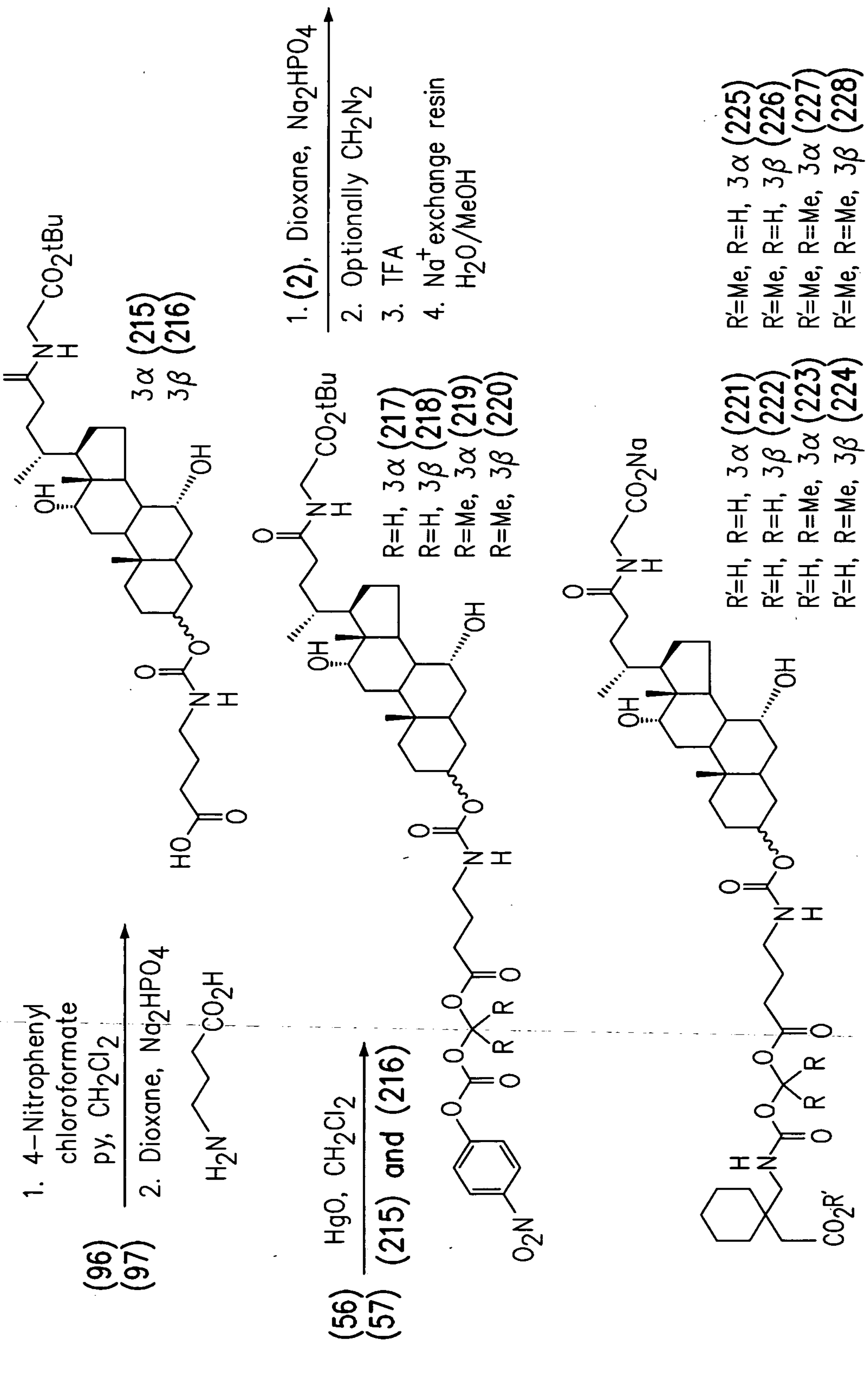

(96)
(97)
1. 4–Nitrophenyl chloroformate py, CH_2Cl_2
2. Dioxane, Na_2HPO_4
H_2N CO_2H
HO
OH
OH
CO_2tBu
3α (215)
3β (216)
(56)
(57)
HgO, CH_2Cl_2
(215) and (216)
O_2N
R R
R=H, 3α (217)
R=H, 3β (218)
R=Me, 3α (219)
R=Me, 3β (220)
1. (2), Dioxane, Na_2HPO_4
2. Optionally CH_2N_2
3. TFA
4. Na^+exchange resin H_2O/MeOH
CO_2R'
CO_2Na
R'=H, R=H, 3α (221)
R'=H, R=H, 3β (222)
R'=H, R=Me, 3α (223)
R'=H, R=Me, 3β (224)
R'=Me, R=H, 3α (225)
R'=Me, R=H, 3β (226)
R'=Me, R=Me, 3α (227)
R'=Me, R=Me, 3β (228)

FIG. 32

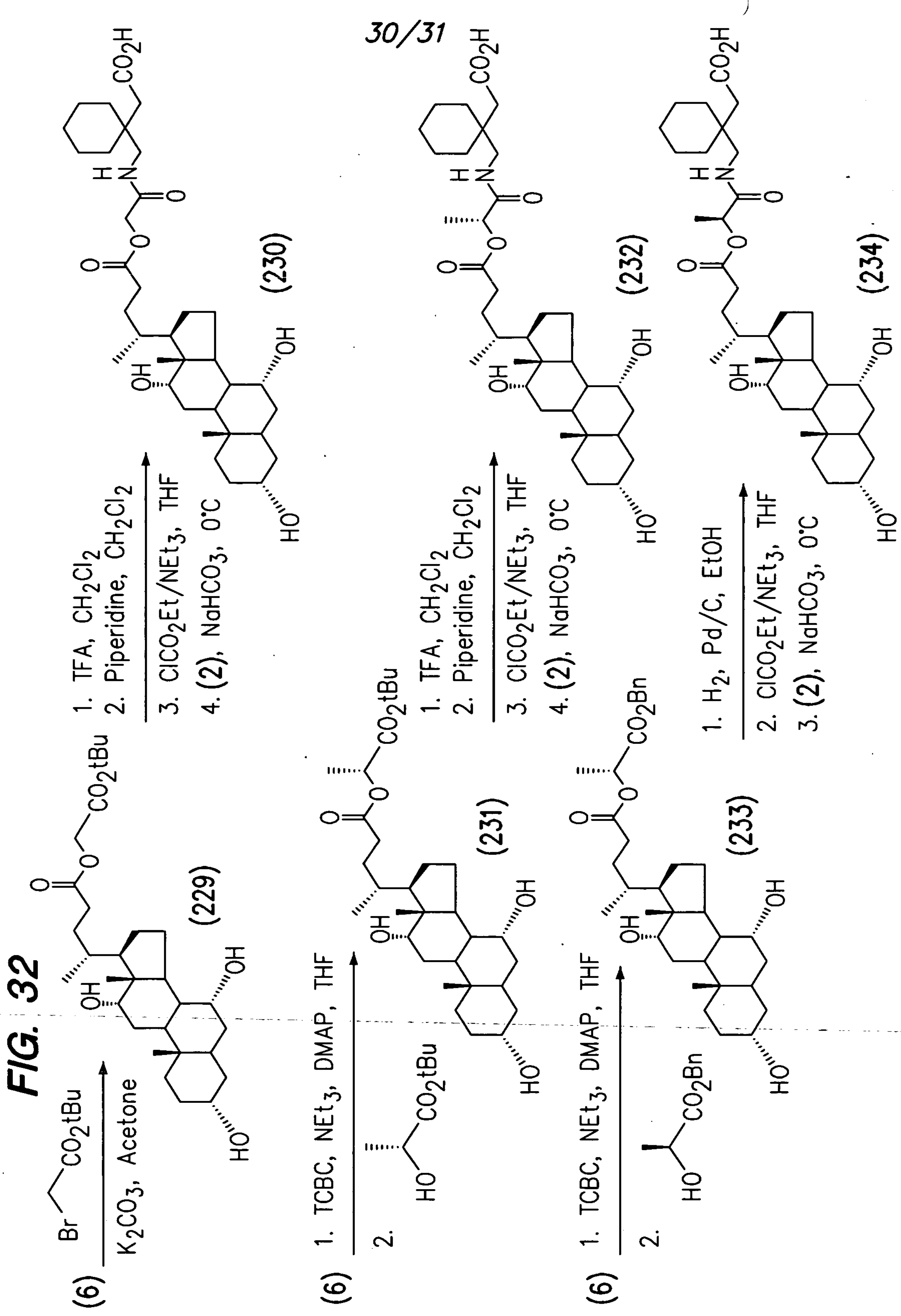

(6)
Br CO2tBu
K2CO3, Acetone
(229)
1. TFA, CH2Cl2
2. Piperidine, CH2Cl2
3. ClCO2Et/NEt3, THF
4. (2), NaHCO3, 0°C
(230)
(6)
1. TCBC, NEt3, DMAP, THF
2. HO CO2tBu
(231)
1. TFA, CH2Cl2
2. Piperidine, CH2Cl2
3. ClCO2Et/NEt3, THF
4. (2), NaHCO3, 0°C
(232)
(6)
1. TCBC, NEt3, DMAP, THF
2. HO CO2Bn
(233)
1. H2, Pd/C, EtOH
2. ClCO2Et/NEt3, THF
3. (2), NaHCO3, 0°C
(234)

FIG. 33